SYNTHESIS OF NITROGENOUS COMPOUDS (SYNTHESIS OF α, β - DIAMINO ACIDS)

THESIS SUBMITTED TO
THE ALIGARH MUSLIM UNIVERSITY ALIGARH
FOR THE AWARD OF THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTY

BY

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August, 1979

ABSTRACT

A general method for the synthesis of α,β-diamino acids from azlactones is discussed. Treatment of azlactones with anhydrous formic acid at reflux temperature gives high yields of substituted pyruvic acids with one more carbon atom. These compounds can also be prepared by the hydrolysis of azlactones with sodium hydroxide solution (15%) to form α-N-benzoylamino-acrylic acids, which when refluxed with phosphorous pentachloride affords α-N-benzoylaminoacryloyl chloride. This on treatment with potassium cyanide solution (10%) and sucessive hydrolysis using hydrochloric acid (20%) yields 3-substituted pyruvic acid. Catalytic reduction of these 3-substituted pyruvic acids converts them into α-amino-β-N-benzoylamino acids in the presence of palladium on carbon (10% Pd) as a catalyst in ethanol and ammonia solution (Sp. gr. 0.99) at elevated hydrogen pressures. The resulting α-amino-β-N-benzoylamino acids could then be hydrolysed directly to α,β-diaminomonocarboxylic acids by using a variety of conditions.

AZLACTONES

Azlactones used in this work were prepared by condensing carbonyl compounds with hippuric acid in the presence of acetic anhydride and different base catalysts.

Sodium acetate was used in the synthesis of 2-2-phenyl-4-(4'-methoxybenzal)-5-oxazolone (80%), 2-phenyl-4-(3'-methoxy-4'-acetoxybenzal)-5-oxazolone (75%), 2-phenyl-4-cinnamylidene-5-oxazolone (60%), 2-phenyl-4-(2'-methoxybenzal)-5-oxazolone (75%), 2-phenyl-4-(4'-acetoxybenzal)5-oxazolone (80%), 2-phenyl-4-(4'-dimethylaminobenzal)-5-oxazolone (69.2%), 2-phenyl-4-(3',4'-dimethoxybenzal)-5-oxazolone(71%), 2-phenyl-4-(2',4'-diacetoxybenzal)-5-oxazolone (91.2%), 2-phenyl-4-(2'-furfurylidene)-5-oxazolone (43.3%), 2-phenyl-4-(1'-napthylmethylene)-5-oxazolone (62.8%), 2-phenyl-4-isopropylidene-5-oxazolone (39%), 2-phenyl-4-cyclohexylidene-5-oxazolone (24.6%).

Potassium carbonate was employed for the preparation of 2-phenyl-4-benzal-5-oxazolone (63%), 2-phenyl-4-(2'-acetoxybenzal)-5-oxazolone (71%), 2-phenyl-4-crotonylidene-5-oxazolone (40%).

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This is to certify that the work described in this thesis is original and suitable for submission.

(N.H. Khan)

ACKNOWLEDGEMENT

I wish to express my deep sense of gratitude to Dr. Naseem Hasan Khan whose valuable advice and constant help led to the development of the work described in this thesis.

I am also grateful to Prof. [illegible] Rahman, Head, Department of Chemistry for providing research facilities.

I gladly acknowledge the CSIR, New Delhi for financial assistance.

NAZAMIR MAHMOOD KIDWAI

C O N T E N T S

EXPERIMENTAL

I. PREPARATION OF AZLACTONE

II. B. CYANIDE PROCESS

(a) SYNTHESIS OF N-BENZOYLAMINOACRYLIC ACIDS

(c) SYNTHESIS OF 3-SUBSTITUTED PYRUVIC ACIDS

III. PALLADIUM CHARCOAL (10% Pd) CATALYSED REDUCTION SYNTHESIS OF α-AMINO-β-N-BENZOYLAMINO ACIDS

IV. HYDROLYSIS OF α-AMINO ACIDS

SYNTHESIS OF DL-α,β-DIAMINO ACIDS

PREFACE

Among nitrogenous compounds α,β-diamino monocarboxylic acids are of interest because they are the analogs of β-amino alanine an amino acid which is the lowest substituted member of a series of homologues α,ω-diamino monocarboxylic acid, of which ornithine and lysine are important higher member and because their parent amino acid β-aminoalanine and other diamino acids are found in hydrolysates of antibiotics substances such as viomycin, polymyxin, aerospin etc.

Organic acids in which one or more hydrogen atoms other than that of carboxylic group are replaced by an amino substituent are called amino acids. α,β-Diamino acids are those, which have two amino groups at α and β-positions to the carboxylic function. These compounds possess the general formula $RCH_2-\underset{NH_2}{CH}-\underset{NH_2}{CH}-CO_2H$ where the side chain R may be of diverse composition and structure.

Some diamino acids occur in nature either in free or in combined state with other organic molecules e.g. β-aminoalanine, γ-aminobutyrine, citruline etc. Many of them have been detected as components of antibiotics, among the products of excretion as bacterial decomposition product in shark liver, in snake muscle and in plant.

As diamino acids are components of a number of antibiotics, there is some interest in effective incorporation of other diamino acids in such biological active molecules. Microorganism, which utilize amino acids in their diet can be inhibited by certain amino acids which acts as antimetabolites. There is also possibility that diamino acid may directly inhibit the growth of the parasite through incorporation of diamino acid analogs in the proteins of their hosts. If such is the case, such an approach may lead to an inhibition of cell growth by introducing suitable diamino acid analogs into cancer tissue proteins.

Since polyamides are synthetic proteins, they have advantages as surgical materials and for artificial internal organs. Other application includes use as chelating agent or antioxidants, but these are based on newly synthesised derivatives rather than the common amino acid themselves. At present amino acids are generally thought of as expensive biological material rather than as a simple chemicals and this inhibits the expansion of consumption. Keeping all these points in mind it was thought worthwhile to develop a new and more efficient method for the synthesis of diamino acids which utilises easily accessible and locally available starting materials.

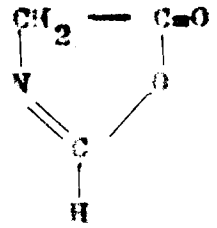
A number of procedures are described in the literature for the synthesis of amino acids but the preparation of diamino acids have not been investigated in great detail. An attempt

has now been made to develop a suitable route for the synthesis of a number of diamino acids using azlactones as intermediate in the synthesis of these compounds. Suitable azlactones are prepared using Erlenmeyer azlactone method.

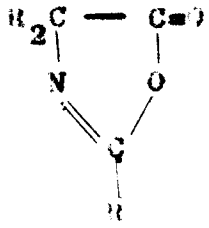
During reduction studies with different reagents we found that treatment of azlactones with anhydrous formic acid at reflux temperature generally gave 3-substituted pyruvic acids in high yields. Thus providing general method for the preparation of substituted pyruvic acid, catalytic hydrogenation of these acids in alcoholic ammonia using palladised charcoal (10% Pd) as catalyst yield α-amino-β-N-benzoylamino acids. Hydrolysis of the α-amino-β-N-benzoylamino acids gives the corresponding α,β-diamino acids.

I. Azlactone Synthesis

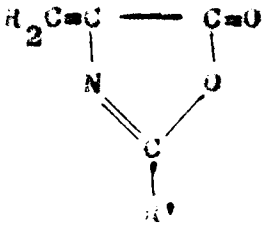
2-Oxazoline-5-ones (1) have also been referred to as 5-oxazolones and oxazol-5-ones. 2,4-Disubstituted, 2-oxazoline-5-ones which are regarded as anhydrides of ∝-acylamino acids, are commonly known as azlactones. They can conveniently be classified into two groups, saturated (2) and unsaturated (3).



(1)



(2)



(3)

Plochl[1] in 1883 prepared the first unsaturated azlactone by condensing benzaldehyde with hippuric acid in presence of acetic anhydride. However, Erlenmeyer determined the structure of this product[2,3]. This reaction was extended to other aldehydes[4-10] to establish the usefulness of unsaturated azlactones as intermediate in the synthesis of ∝-keto acids[11-13] and ∝-amino acids[4,14-18].

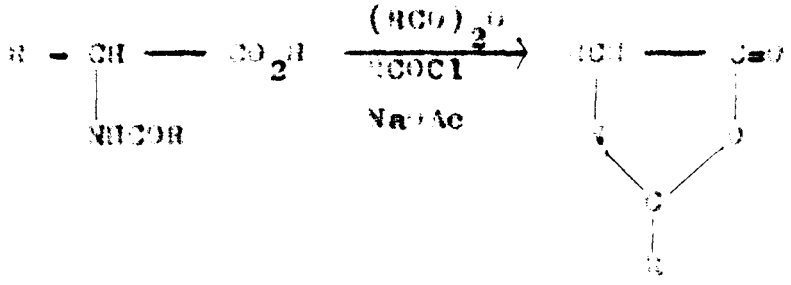
1. Azlactonization of α-acylamino acid

α-Acylamino acids can be converted into azlactone under the following conditions.

(a) Action of an acid anhydride, either alone or in acetic acid as solvent or an α-acylamino acid (or, occasionally a free amino acid)[19-31].

(b) Action of an acid anhydride[30] or acid chloride[32] on the sodium salt of an α-acylamino acid (or free α-amino acid) in aqueous solution.

(c) Action of an acid anhydride or chloride on an α-acylamino acid in pyridine solution[33,34].



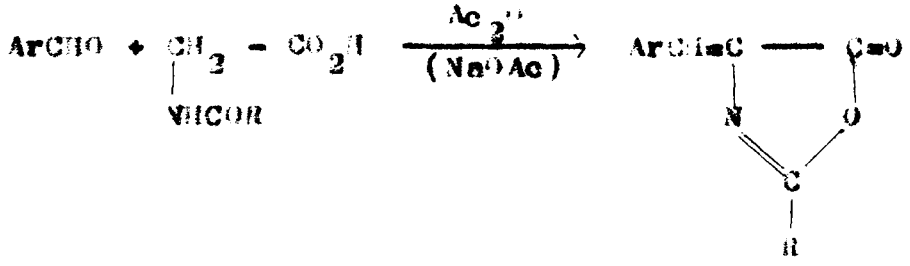
(4)

Of these methods the first is the most convenient and the only one generally[30,34-41] used.

Since the unsaturated acylamino acids are not readily available, none of these methods is useful for the preparation of unsaturated azlactones.

2. Reaction of an aldehyde with an acylglycine in presence of acetic anhydride

The reaction of an aldehyde with an acylglycine in presence of acetic anhydride (and usually sodium acetate) is referred to as the Erlenmeyer azlactone synthesis.

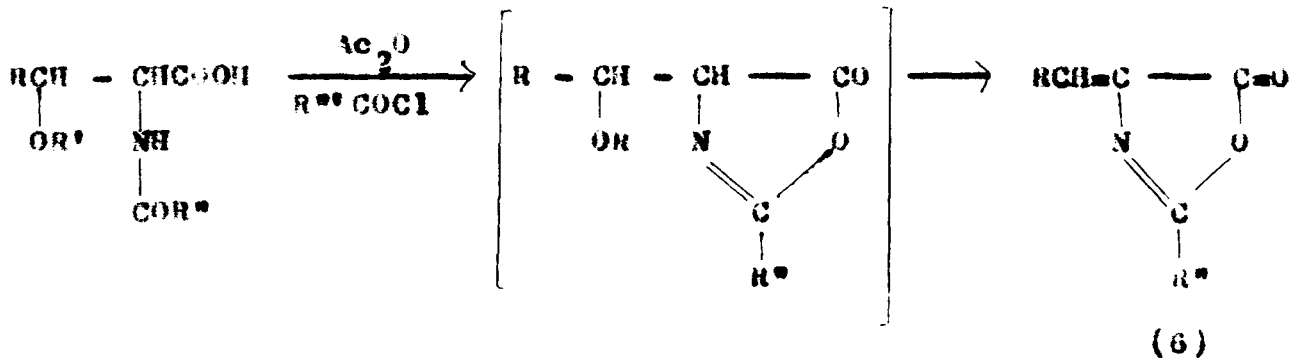


(5)

Erlenmeyer was unable to prepare saturated azlactones probably because he failed to appreciate the ease with which they are hydrolysed[35].

3. Reaction of an α-acylamino-β-hydroxy acid with an acid anhydride or acid chloride

The action of acetic anhydride on an -acylamino- -hydroxy (alkoxy or acyloxy) acid produces an unsaturated azlactone.

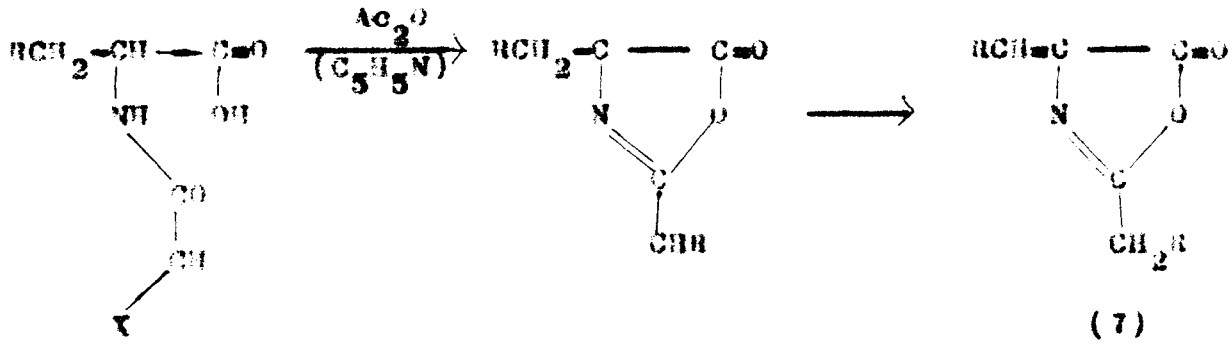


(6)

The first step in this transformation is the conversion of acyl derivative into the corresponding saturated azlactone. This saturated azlactone possesses an extremely active α-hydrogen atom which split out with the β-substituent under very mild condition to form unsaturated azlactone.

4. Reaction of an α-(α'-haloacyl)amino acid with acetic anhydride

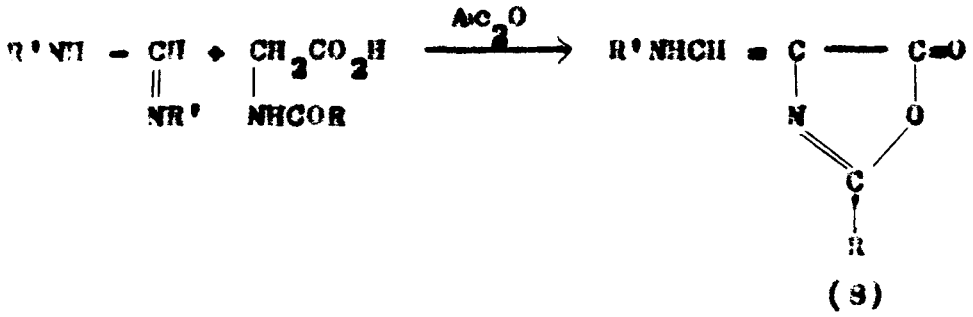
The conversion of an α-(α'-haloacyl)amino acid into an unsaturated azlactone has not been studied extensively. A proposed mechanism is shown in the equation below:



(7)

Besides the above four methods of preparation of azlactones, a number of other methods have also been developed.

Azlactones are also obtained by the reaction of a dialkyl or diarylformamidine with acylglycine and acetic anhydride[38].

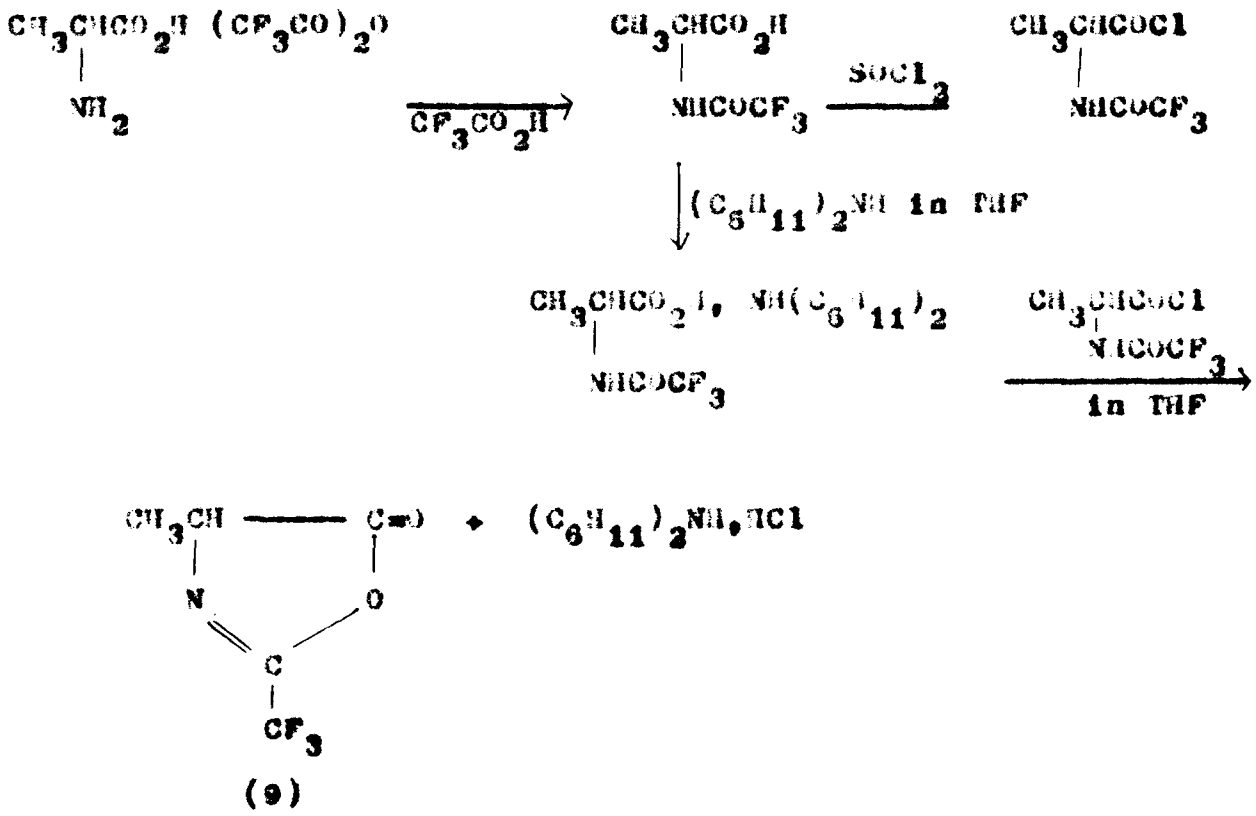


(8)

Potassium carbonate or bicarbonate is an excellent catalyst[37] for the condensation of aldehydes with hippuric acid and is, in several respects, superior to sodium acetate used in the standard procedure.

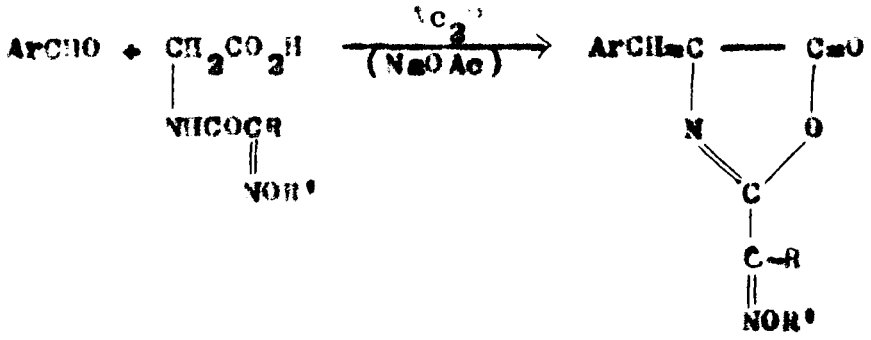
Triethylamine has also been employed as a catalyst in the formation of azlactones[38,42].

Weygand[43] et al. have synthesised 2-trifluoromethyl-4-methyl-5-oxazolone using trifluoroacetic anhydride and anhydrous trifluoroacetic acid as shown in the following equation.



(9)

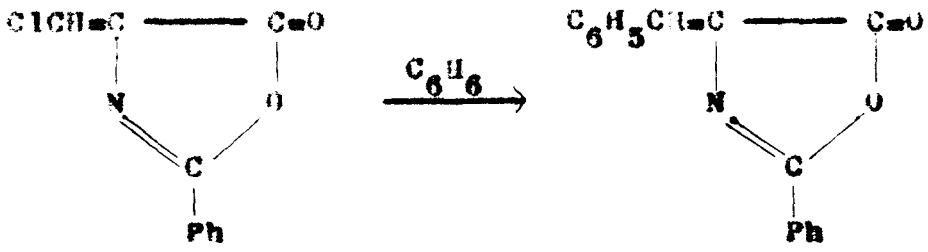
The α-alkyloximino acids combine readily with an arylaldehyde to make available a large number of azlactones[44] using the usual conditions.



(10)

Although aliphatic aldehydes do not readily undergo Erlenmeyer reaction, the lower member react readily in the absence of sodium acetate or acetic anhydride[45] with 2-phenyl-5-oxazolones and its derivatives in a Perkin-Erlenmeyer type reaction.

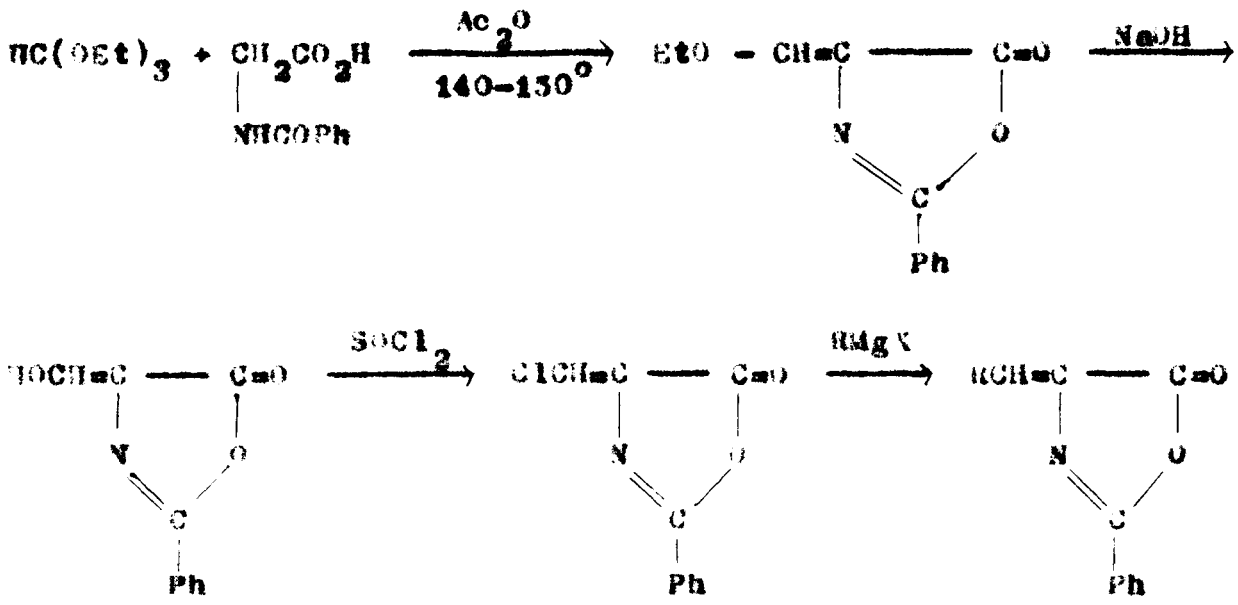
Unsaturated azlactones are prepared from 2-aryl-4-halomethylene-5-oxazolones by reaction with organometallic compounds, compounds with an acidic hydrogen and compounds which undergo Friedel Craft's[46] reaction.



(11)

Synthesis of azlactones have also been effected by cyclodehydration with sulphur trioxide complexes[47].

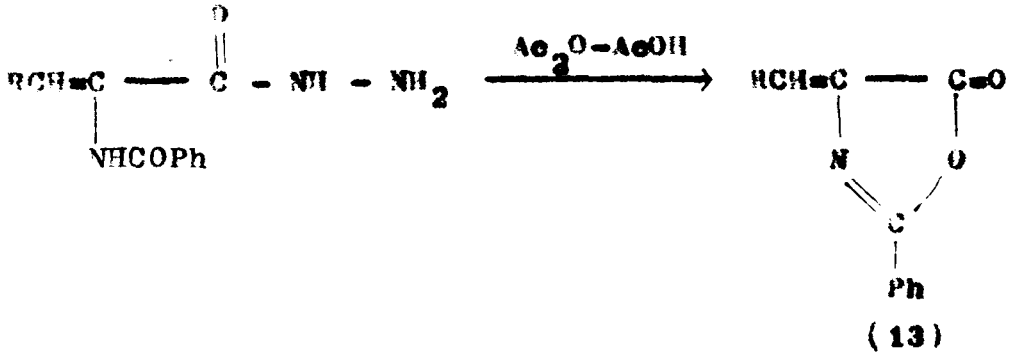
Behringer et al.[49] carried out azlactone synthesis by refluxing a mixture of hippuric acid and ethylorthoformate in acetic anhydride at 140-150° for an hour.



(12)

The cyclization[49] of α-haloacylamino acid to give azlactones have been accomplished by treating with benzoic anhydride and sodium benzoate at 100° or treating with $POCl_3$ and lutidine in CH_2Cl_2 at 15°.

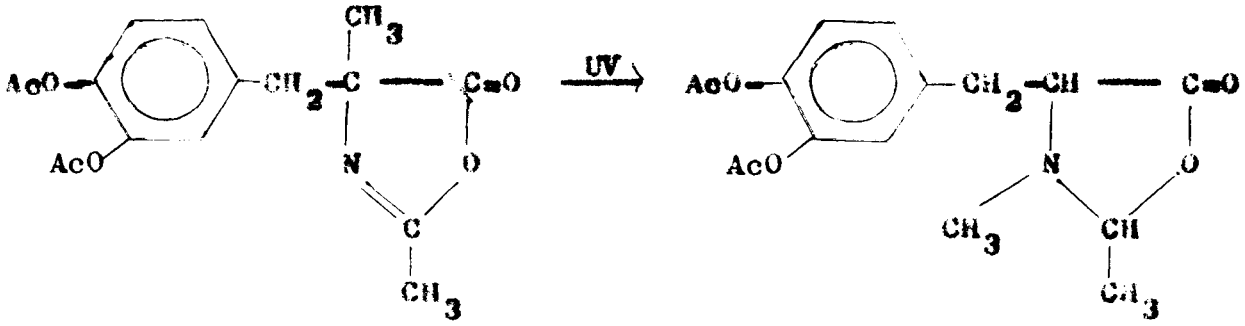
Bodea et al.[50] obtained azlactones by the cyclization of α-acylamino acid hydrazides in presence of acetic acid-acetic anhydride mixture.



(13)

Woodward et al.[51] have reported that the reaction of hippuric acid with isoxazolium salt to give enol esters was accompanied by azlactone formation.

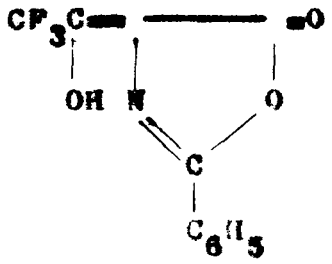
Harry et al.[52] have been successful in converting one azlactone into another by exposure to ultraviolet light.



(14)

A solution of D(+) 2,4-dimethyl 4-(3',4'-diacetoxybenzyl) 5-oxazolone in dioxane was irradiated for 6 days in quartz flask with high pressure mercury arc ultraviolet lamp. The solvent was removed in vacuo to yield DL-2,3-dimethyl 4-(3',4'-acetoxybenzyl)-5-oxazolone.

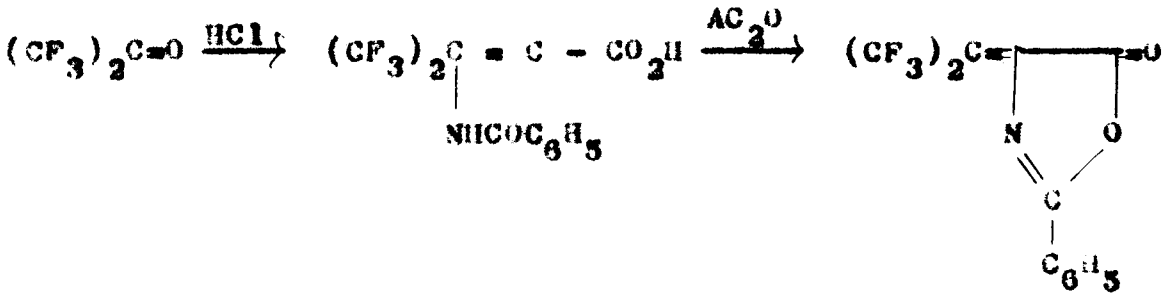
The reaction of hippuric acid with three fold excess of trifluoroacetic anhydride gives a 90 percent yield of 2-phenyl 4-(2',2',2'-trifluro) 1'-hydroxyethylidene-5-oxazolone (15)[53].



(15)

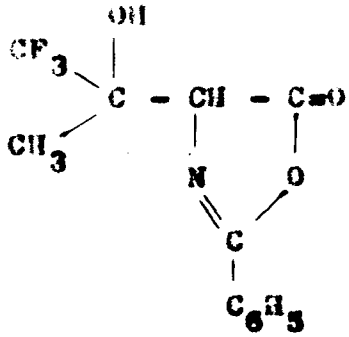
This compound is also obtained in high yield by the interaction of $(CF_3CO)_2O$ with 1. In contrast to the behaviour in acetic anhydride[54] the later reaction proceeds in the absence of nitrogen base.

A number of unusual aliphatic trifluoromethyl compounds have been obtained from 4-hexafluoroisopropylidene-2-phenyl-5-oxazolone (16)[55].



(16)

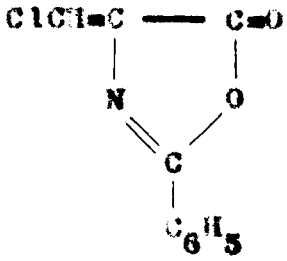
This is borne out by observation[56] that trifluoroacetone and hippuric acid give a mixture of diastereomers of the saturated azlactone (17) in acetic anhydride-acetate medium.



(17)

A new synthesis of unsaturated azlactones which is especially useful in cases, where aldehyde is not readily available has been developed[48]. The reaction involves the nucleophilic

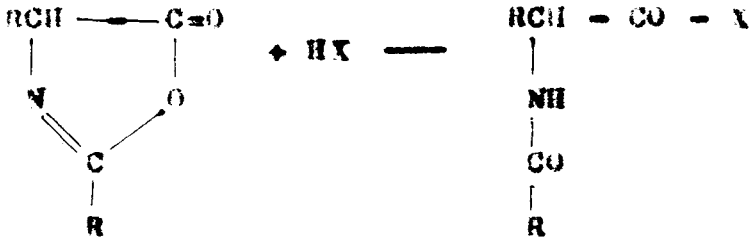
displacement of chlorine in 4-chloromethylene-2-phenyl-5(4H)-oxazolone (18)[57] by hydrogen compound, usually activated by formation of organometallic reagent. Recently[58] azlactone is prepared from N-oxa-alkylidene carboxamide.



(18)

II. Reactions of Azlactones

Azlactones behave in many respect like acid anhydrides and react with a wide variety of compounds such as water, alcohols, amines and hydrogen halides, which contain active hydrogen atoms. As with acid anhydride, reaction occurs most readily with amines, less readily with alcohols and least readily with water.



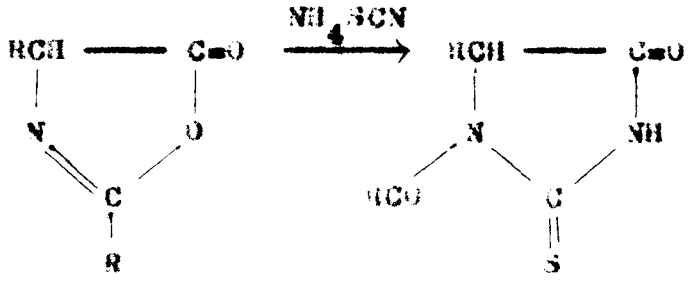
(19)

(X=NH_2, -NHR, $-NR_2$, -OR, -OH and halogen)

The saturated azlactones are much more reactive than the unsaturated compounds. The unsaturated azlactones can be recrystallized from boiling ethanol and are not altered by long contact with water, whereas the saturated compounds are slowly hydrolysed by water at room temperature and react even more readily with ethanol.

1. Reaction with Ammoniumthiocyanate

Saturated azlactones are converted into thiohydantoins by ammoniumthiocyanate[60-62], whereas unsaturated azlactones do not react with the reagent[60].

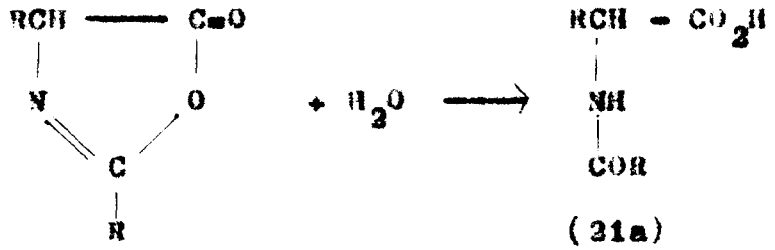


(20)

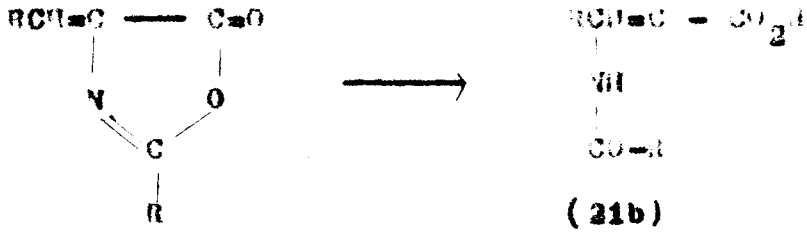
Unsaturated azlactones are relatively stable to heat, whereas saturated azlactones undergo condensation reaction, often at room temperature. During this process liquid azlactones are converted into clear semi-solid waxes. The nature of the substituent has a marked effect on this reaction.

2. Hydrolysis

Azlactone can be hydrolysed to the corresponding acid with alkaline or acidic[33] reagents. Thus 2-methyl-4-benzyl-5-oxazolone is hydrolysed by water at room temperature[27]. 2-Methyl-4-benzal-5-oxazolone by boiling aqueous acetone[39] or by boiling 1% aqueous sodium hydroxide[12] solution.



(21a)

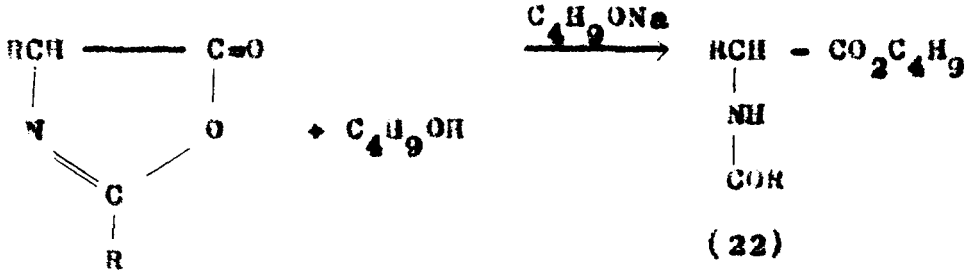


(21b)

3. Alcoholysis

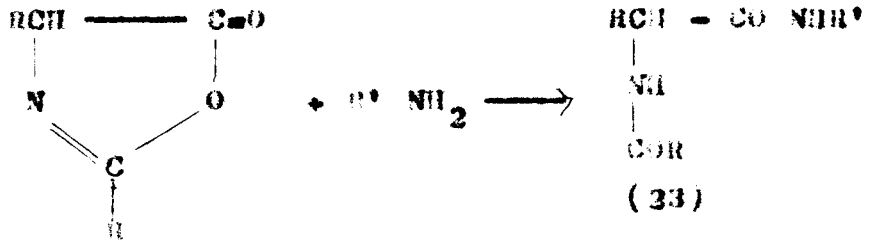
Unsaturated azlactones ordinarily do not react with hot alcohol. However, if either an acid[12,63] or a base is added to the ethanol, the oxazolone ring is opened rapidly with the formation of α-acylaminoacrylic ester. With sodium hydroxide or alkoxide the reaction is complete in three to five minutes at room temperature[6,7,31,64,65] with sodium carbonate as catalyst,

a short period of refluxing is required[66-67]. Azlactones also react rapidly with higher alcohols in presence of sodium alkoxide[64].



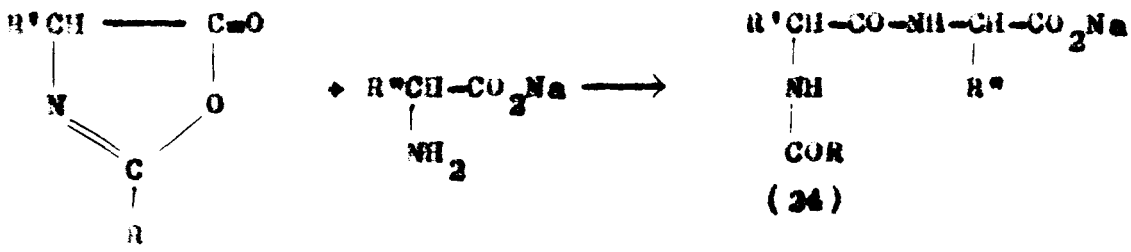
(22)

Saturated azlactones react quite vigorously with ammonia and amines[19,22,27,30,68].



(23)

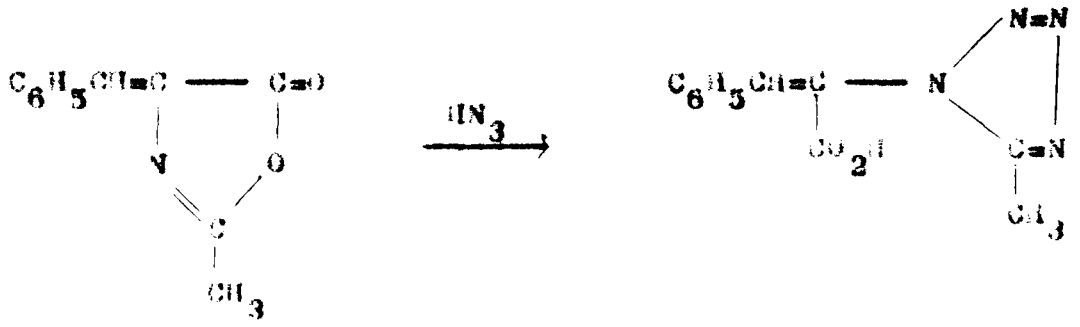
The reaction usually is effected by treating the azlactone with pure amine at room temperature. Sometime with longer reaction time[27,69,70,71]. Excellent results are obtained with unsaturated and saturated azlactones using aqueous acetone containing an equivalent amount of sodium hydroxide along with amino acid.



(24)

4. Azidolysis

Both saturated and unsaturated 5(4H)-oxazolones behave as cyclic O-acylimino-ether on reaction with hydrazoic acid giving substituted tetrazolcarboxylic acids[72] by alkyl cleavage and cyclization of the unstable imidazide. There is no evidence for the presence of acid azide amides, the products of the alternate acyl ring fission. Thus compound (25) is converted in nearly quantitative yield to (5-methyl-1-tetrazoyl) cinnamic acid (14).



(25) (26)

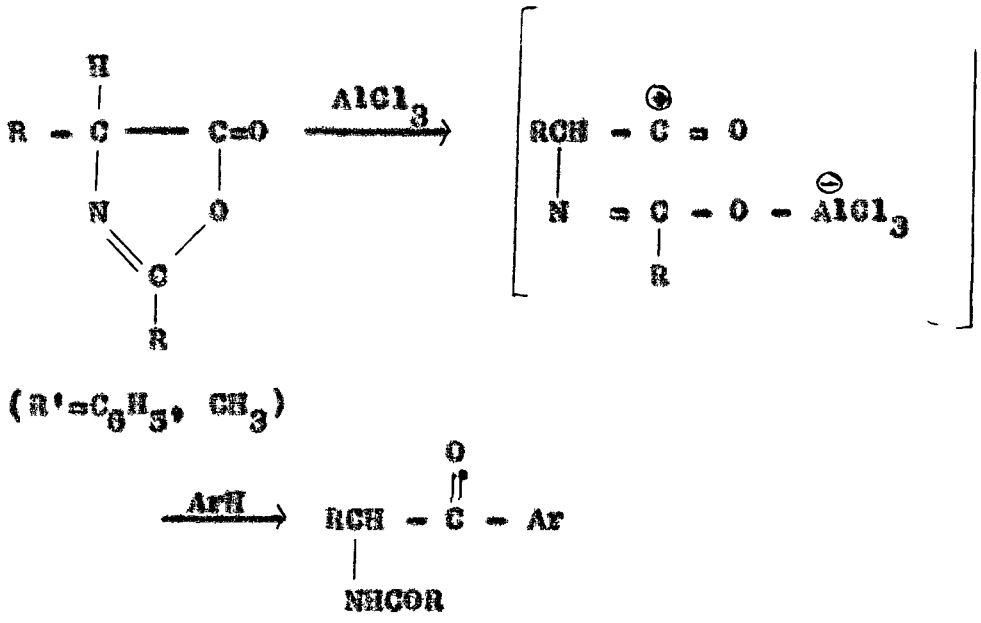
5. Acylation

A. Reaction with Phosphate anions

Saturated azlactones behave as acyl donors and react with orthophosphate in aqueous pyridine to give quantitative yields of acylphosphate which are of biological interest[73].

B. Behaviour under Friedal-Craft condition

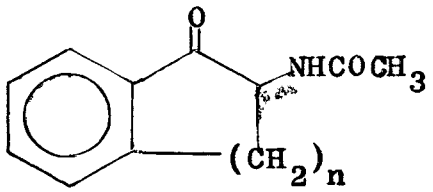
Saturated azlactones react with aromatic hydrocarbon in the presence of anhydrous aluminium chloride to give acylamino ketones[74] in high yields.



(R'=C_6H_5, CH_3)

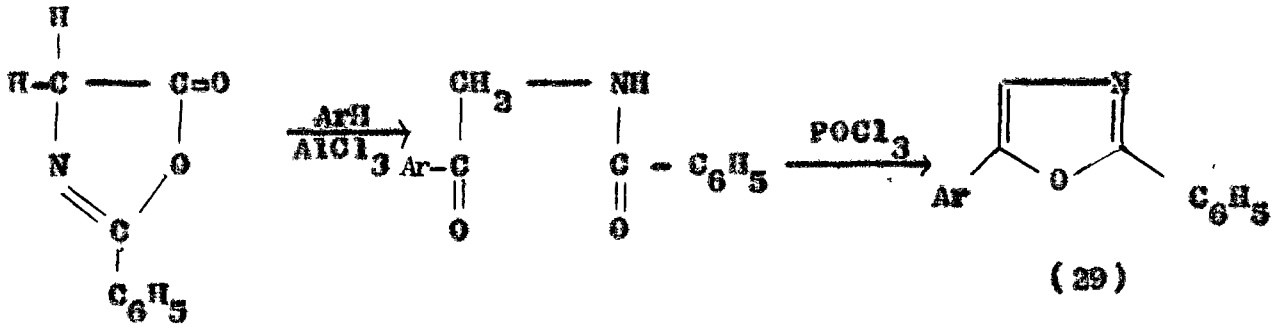
(27)

When R is benzyl, $C_6H_5CH_2CH_2$ or $C_6H_5CH_2CH_2CH_2$ these intermolecular reactions are accompanied by intramolecular acylation to form cyclic amino ketones (28)[75].



(28) n=1, 3 or 3

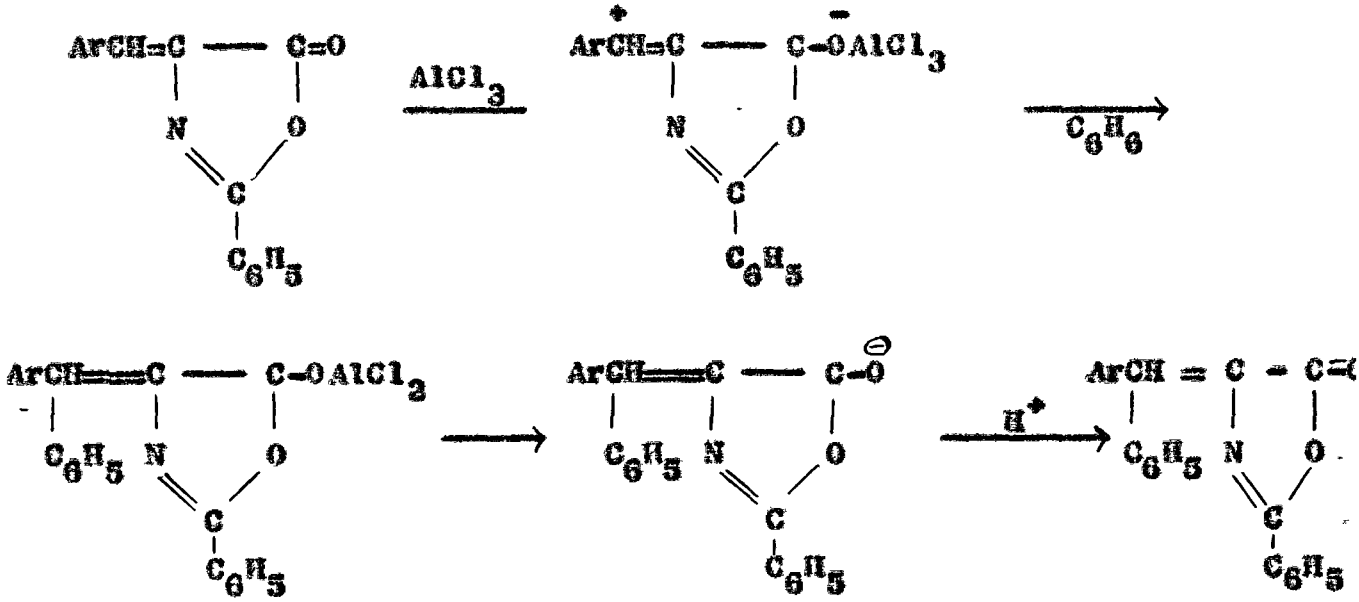
The open chain acylamino ketone may be cyclized in 85-95 percent yields, and this is a good synthetic route to 2,5,diaryl oxazoles[76-77].



(29)

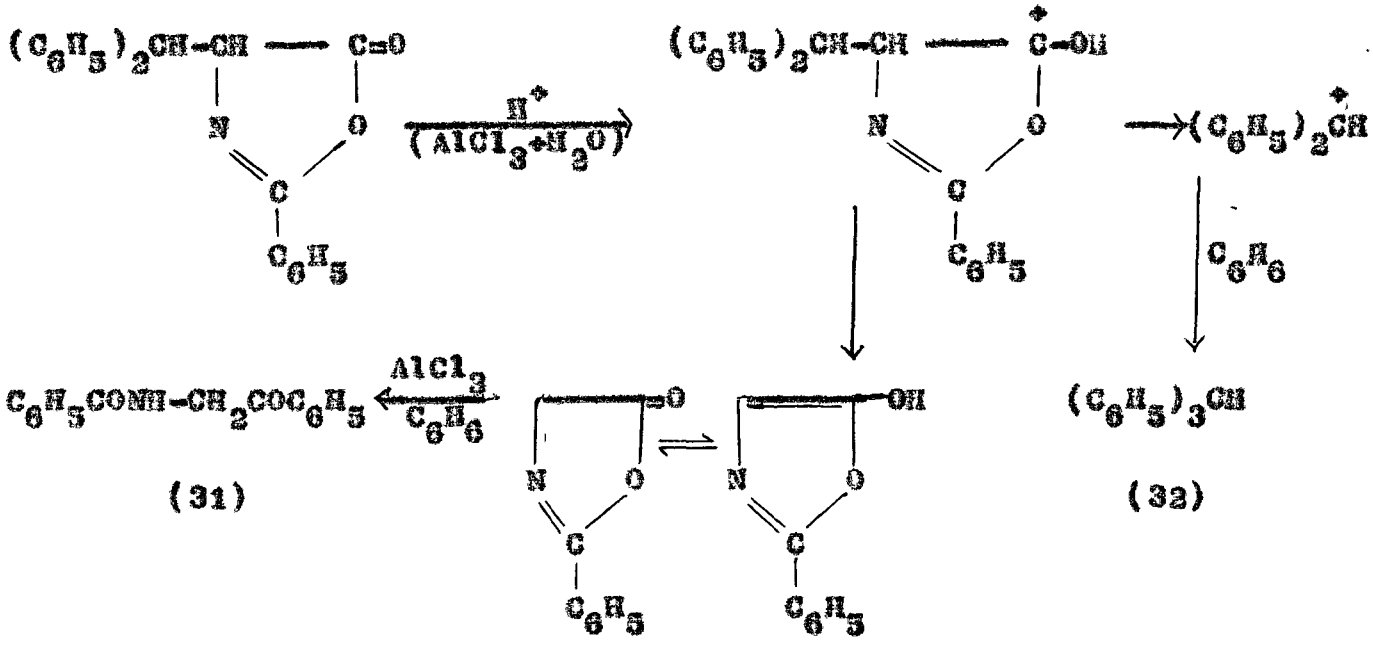
The reaction has been investigated[78-82] in considerable detail and the following conclusions have been drawn:

(a) In benzene, toluene, chlorobenzene and anisole, the product reflect participation of the solvent as a reactant, whereas in inert solvent two type of products formed by intramolecular processes are isolated.

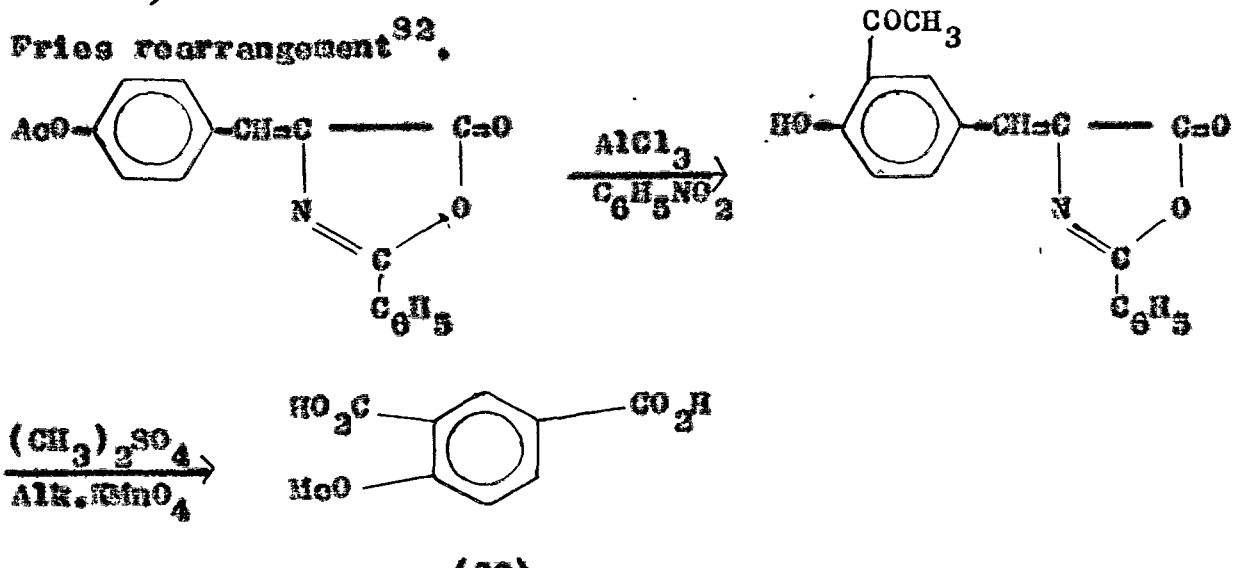


(30)

(b) In the presence of freshly sublimed aluminium chloride and under anhydrous condition, compound such as 11 react with benzene to form 1,4-addition product, the saturated azlactone(30), in 70-75 percent yield. If moisture is not excluded fragmentation of saturated azlactone occurs to give, after acylation, ω-benzamidoacetophenone (31) and triphenylmethane (32)[79-81].

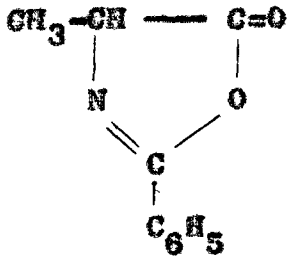


(c) There is usually no reaction with nitrobenzene as solvent. However, in this medium acetoxybenzylidene azlactones undergo a Fries rearrangement[82].



6. Reaction with Grignard Reagents

4-Methyl-2-phenyl-5-oxazolone (34) reacts with excess of phenylmagnesium bromide to give 2-benzamido 1,1-diphenyl-1-propanol (35) with excess ethylmagnesium bromide (34) forms N,N'-dibenzoyl-3,6-dimethyl 2,5-diketo piperazine[83](36).



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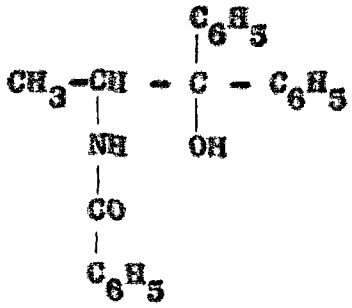
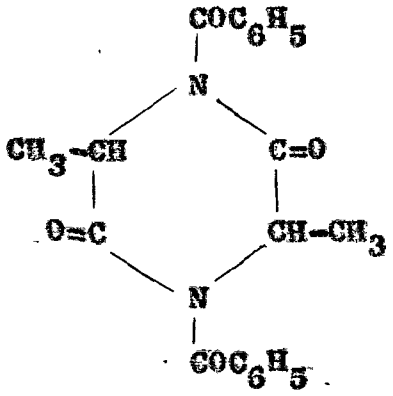
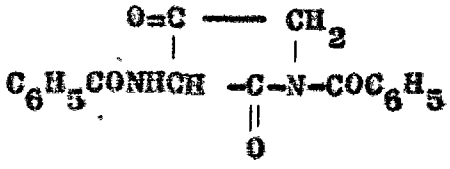


(35)

Compound (22) however, is converted into a complex mixture[84] from which the dimeric acid, 3-benzamido-1-benzoylpyrrolidene-2,4-dione (37) has been isolated.



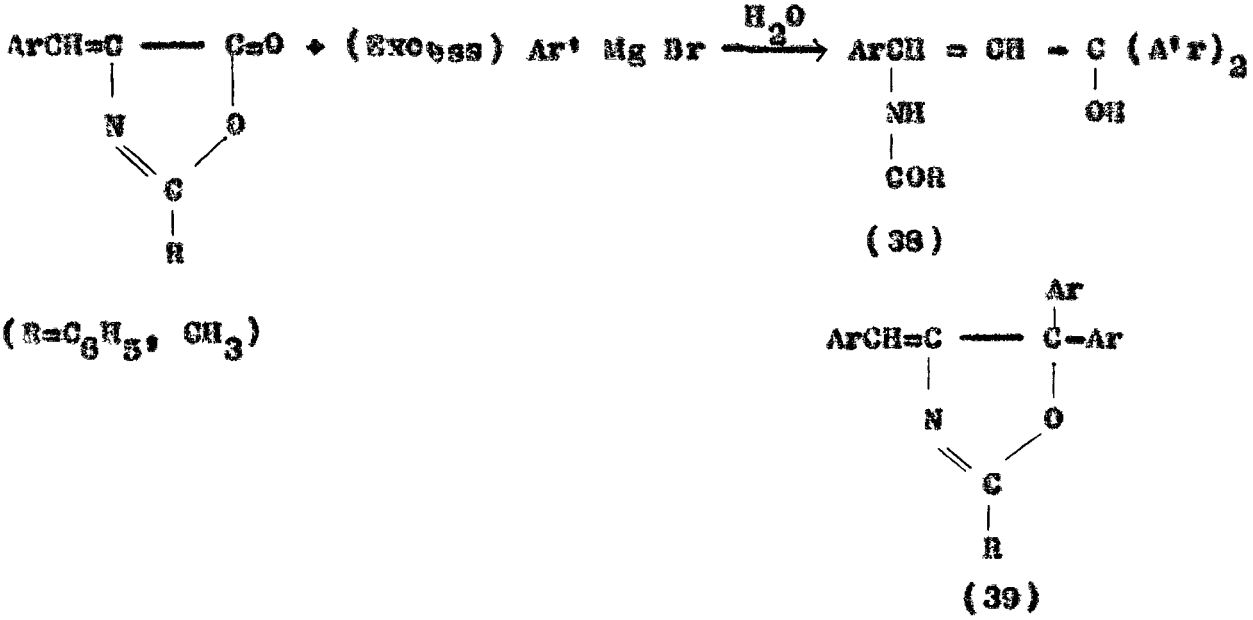
(36)



(37)

The behaviour of unsaturated azlactones with organo-metallic compounds have been studied in detail[85-93].

Arylmagnesium halides and phenyllithium attack 4-arylidene-5-oxazolones at the carbonyl carbon to give open ring amido-tertiary alcohol (38) and oxazolines (39) usually as mixtures[85-87] The nature of the Grignard reagent[87] and dilution factors[87] determine the ratio of the products and in some cases one product is formed exclusively[89]. The alcohols cyclize to the oxazolines with acetic anhydride[37,88] and to substituted indone[88](40) with hydrochloric acid-acetic acid mixture.

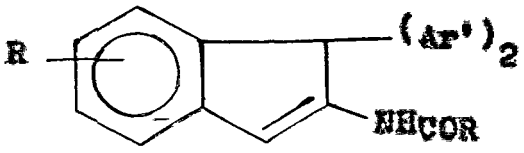


(R=C_6H_5, CH_3)

(38)

(39)

When compound 11 is treated in a 1:1 ratio with phenylmagnesium bromide using inverse addition[87], the reaction is sluggish and stops at the ketone stage giving -benzamidobenzal acetophenone (41).



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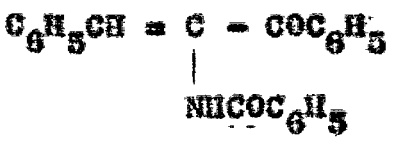
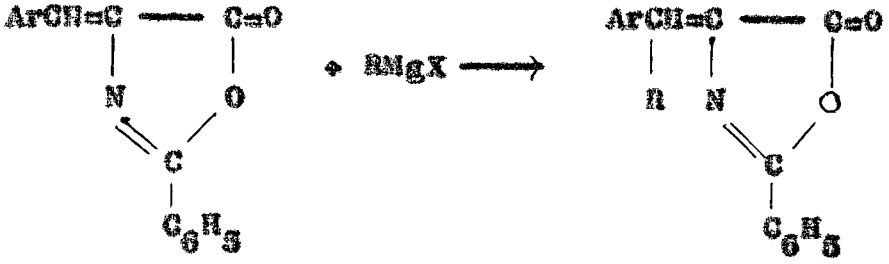


(41)

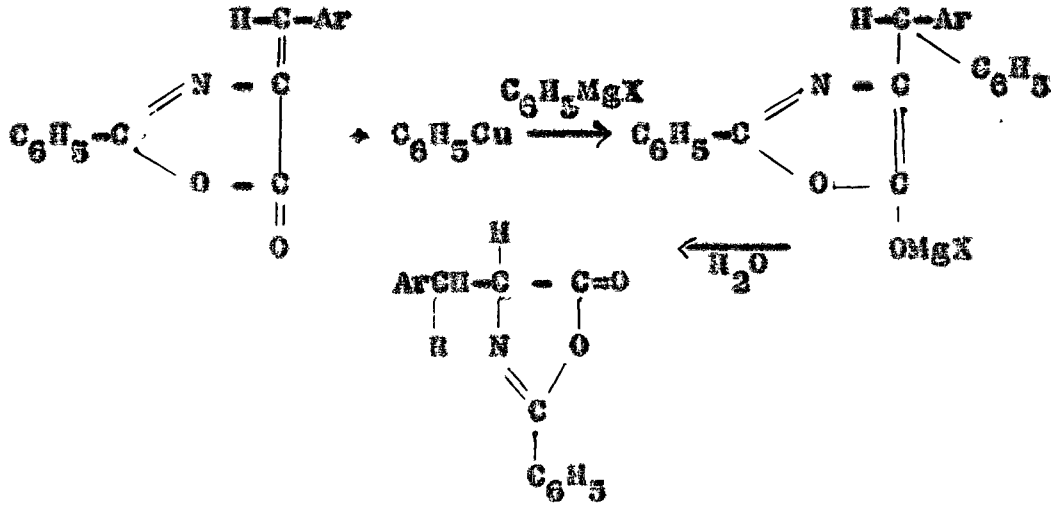
In contrast to these ring opening reactions it was observed by Horner and Schwahn[90] that 4-arylidene (Isopropylidene and cyclohexylidene) oxazolones react with alkyl Grignard reagent by conjugate addition to give saturated azlactone (41a) as the only product.



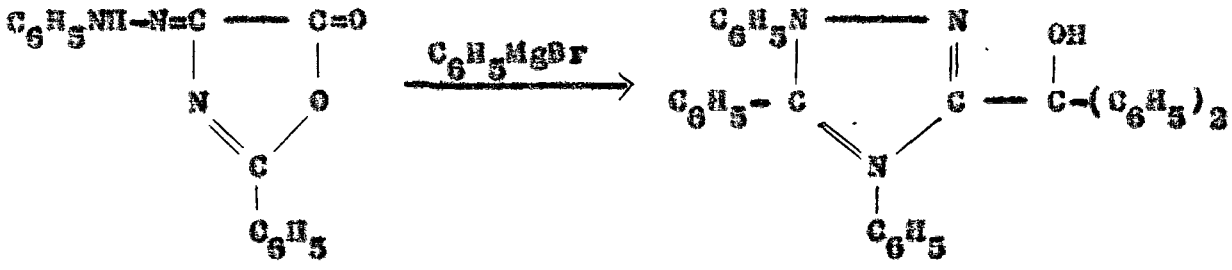
(41a)

Filler et al.[91] noted that the labile geometric isomer of 11 gives saturated azlactones (30) in 35-40 percent yield as well as products of 1,2 addition, when treated with several arylmagnesium bromides. Earlier report[94-95] showed that conjugated addition of Grignard reagent to α,β-unsaturated carbonyl system was enhanced by cuprous chloride. This reaction was studied[93] with a large number of 4-arylideneoxazolones and variety of arylmagnesium halides. The addition of $CuCl_2$ to the Grignard reagent in a 2:3 mole ratio markedly alters the course of the reaction and leads to the predominant formation of saturated azlactone. The yield of these product generally range from 50-75 percent.

$$2C_6H_5MgBr + CuCl_2 \longrightarrow 2C_6H_5Cu + 2MgBrCl$$



4-Arylazo-2-phenyl-5-oxazolone (42) is converted to 1,2,4 triazole by the action of phenylmagnesium bromide[93].



(42)

7. Amino Acid and peptide synthesis

Saturated azlactones such as (30) and (41a) are useful intermediates for the synthesis of a variety of β,β-disubstituted alanines (43)[90,96].

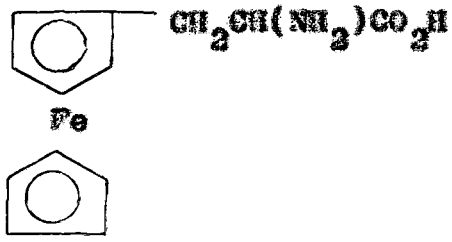
$ArCHR — CH(NH_2)CO_2H$

R=alkyl or aryl

(43)

The azlactones are first hydrolysed with alkali to N-benzoyl amino acids and then to (43) using an hydrogen bromide and acetic acid mixture.

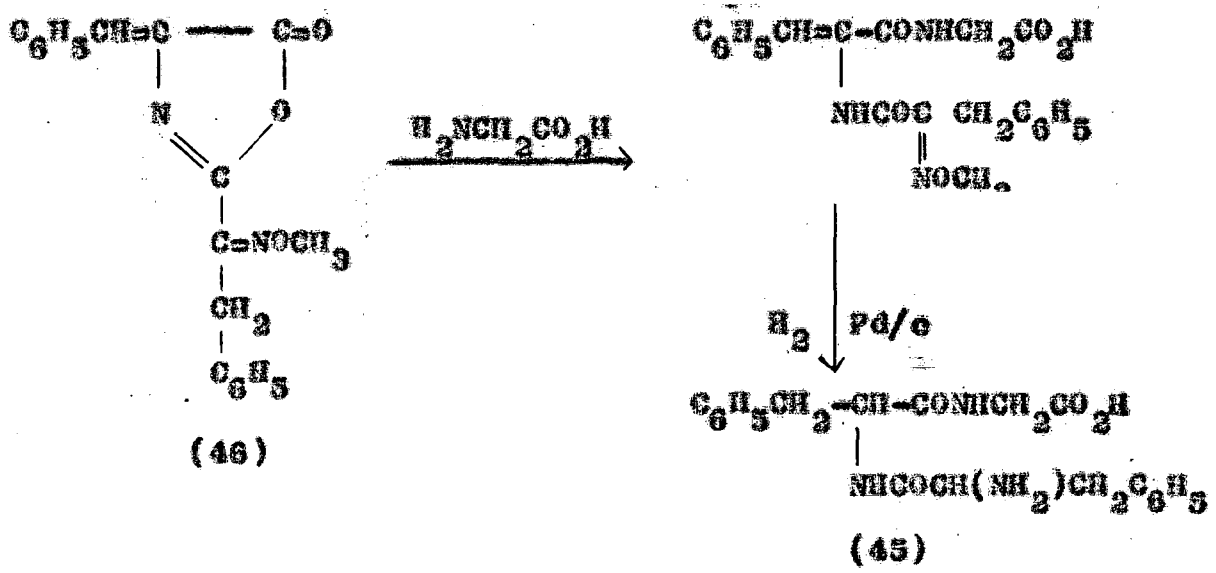
A number of new β-substituted alanines have been prepared from unsaturated azlactones by the usual reduction-hydrolysis procedure. An interesting example is the synthesis of DL-β-ferrocenylalanine (44)[97,98].



(44)

The synthesis of γ-hydroxy valine and γ-γ-dihydrovaline via azlactone has been reported by Galanta and Szabo[99].

An interesting new synthesis of tripeptide DL-phenylalanyl-phenylalanylglycine (45) from oxazolone (46) has been reported[44].

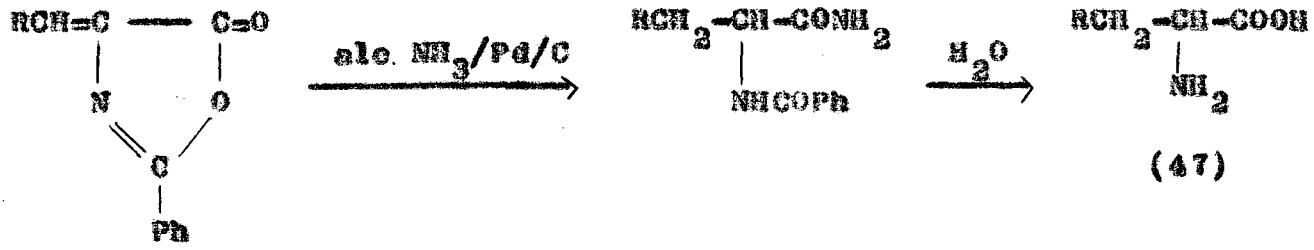


(46) (45)

A survey of the literature revealed that the unsaturated azlactones and their acylaminoacrylic acids were converted to α-amino acids by reduction and hydrolysis. Reductions were accomplished by chemical method using sodium[118,119], sodium amalgam[12-14,36-39,41-54,64,100-111] or sodium lead alloy[112] in water or ethanol or sodium borohydride alone[113]. But chemical reduction was not always satisfactory, as some azlactones were not reduced at all[114-115] while in other cases yield were often very low[116-119]. Hydriodic acid with red phosphorous in acetic acid or acetic anhydride[120-134] has also been employed for the synthesis of most of the amino acids. But this method causes difficulties as the isolation of amino acids is difficult and methoxy derivatives could not be synthesised by this method. Reduction with zinc in acetic acid[135-137] has also been used in few cases. Thus Sacrolysine[135], p-[bis-(o-chloroethyl)amino]

phenylalanine[137] were synthesised by this procedure. Finally electrolytic reduction was used in the synthesis of 3,4-dihydroxyphenylalanine only[138] and catalytic hydrogenation followe by hydrolysis has been used to a limited extent[17,139-144]. Platinum[144], palladium[124,126,140] and Raney nickel[17,139,142] were the catalysts so far employed for this purpose.

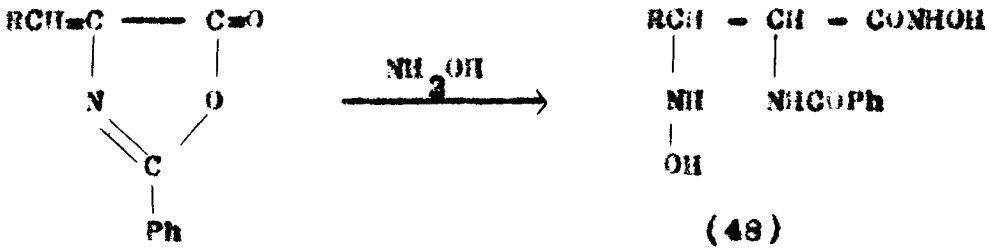
It has been shown that azlactones can be directly converted to the N-benzoylamino acid amides in high yields and with greater purity by catalytic reduction in the presence of palladium charcoal and alcoholic ammonia at elevated hydrogen pressure and room temperature, the resulting amides can be converted directly to the required α-amino acids[18](47).



(47)

Recently Rathshinda et al.[145] introduced 2-phenyl-4-benzal-5-oxazolone as starting material in β-aminophenylalanine formation in our laboratory. Treatment of azlactone (I) with hydroxylamine gives α-N-benzoyl amino-β-hydroxylamino hydroxamic acid (48) which can be used as intermediate for the preparation of α,β-diamino acids. The main drawback of this reaction is that other undesirable products like α-N-benzoylamino

hydroxamic acid (49) and α,α-dibenzoylamino disubstituted hydroxamic acid (50) are also obtained during the course of the reaction and difficulties are encountered to isolate β-hydroxylaminohydroxamic acid.



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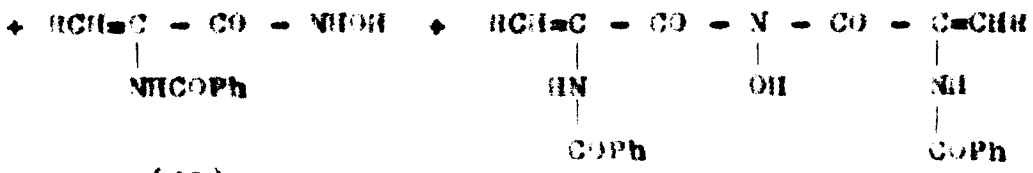
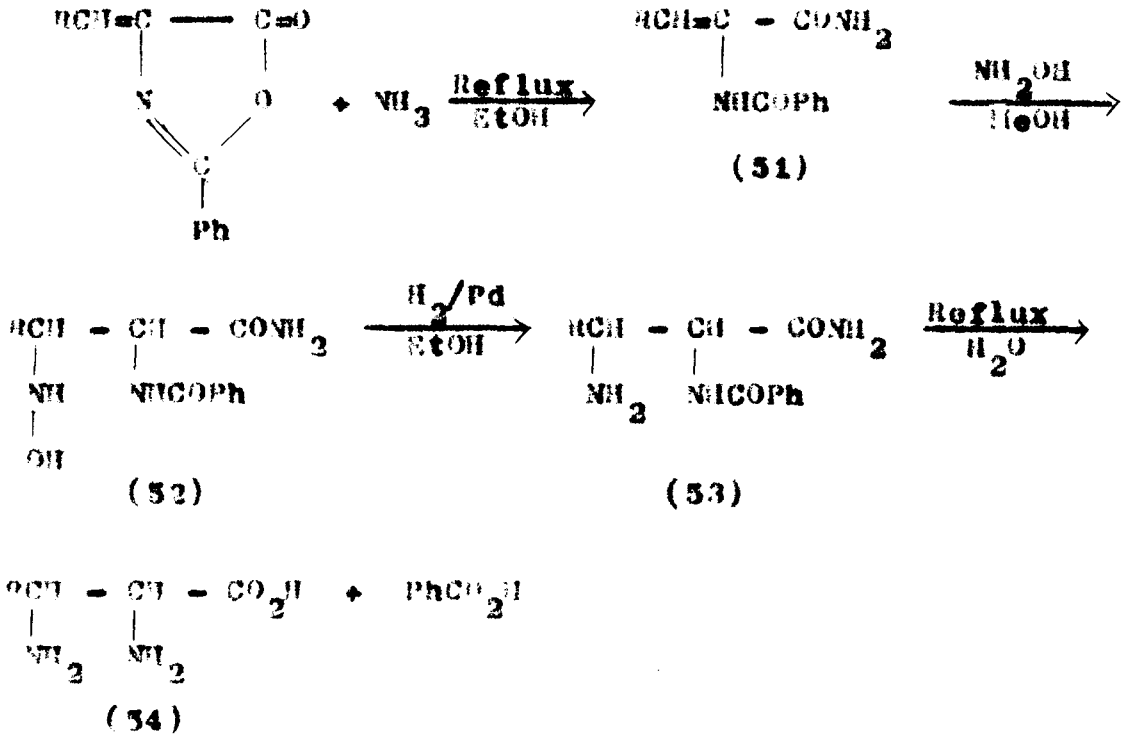


(49)

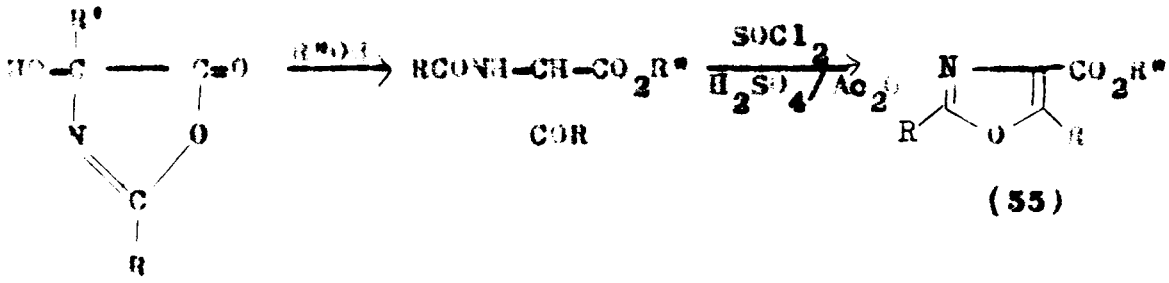
(50)

They modified the above mentioned method[146] by ammonolyzing azlactone (1) to yield α-N-benzoylaminoacrylic acid amides (51) in good yield which when treated with hydroxylamine gave α-N-benzoylamino-β-hydroxylamino acid amides (52) catalytic reduction of compound (52) in ethanol using palladium charcoal (10% Pd) catalyst gives α-N-benzoylamino β-amino acid amides (53). Hydrolysis of these amides (53) produced the required α,β-diamino acids (54).

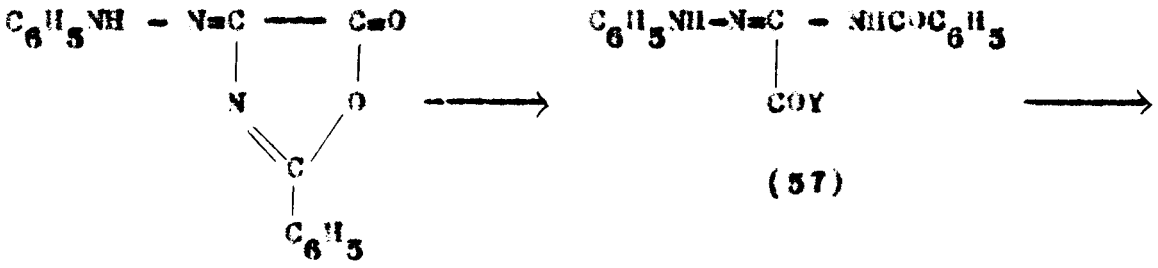


3. Conversion into other Nitrogen Heterocycles

The hetero ring in 4-(1'-hydroxyalkylidene)-5-oxazolones is cleaved by alcoholic hydrochloric acid to form alkyl - acylaminoacylacetates, which cyclize to oxazole-4-carboxylates (55)[147]. This rearrangement occurs directly in alkali and a carbon-14 tracer study has substituted mechanism involving ring opening followed by alternative ring closure[148].



The conversion of 4-arylazo-5-oxazolone into 1,2,4-triazole by the reaction of Grignard reagent is discussed[93]. In similar fashion the rearrangement of compound (42) to derivatives of 3-carboxy-1,5-diphenyl. 1,2,4-Triazoles (56) proceeds readily in the presence of strong nucleophiles[149]. The transformation undoubtedly occurs by ring opening and dehydrative cyclization, and, indeed the cyclic amide and hydrazide (57) have been isolated[150].



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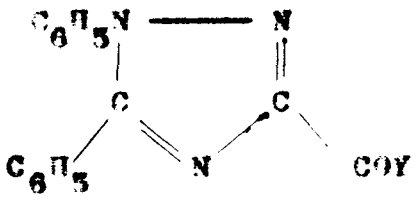


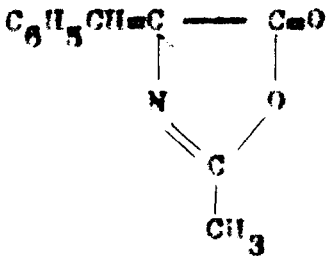
(56)

Y = OCH_3, NH_2, $NHNH_2$

9. Miscellaneous Reactions

When 4-benzylidene-2-methyl-5-oxazolone (58) is prepared by Erlenmeyer procedure, a light yellow product is generally isolated. Rufenacht[151] showed that pure (58) is white and that the coloured contamenant is 4-benzylidene-2-styryl-5-oxazolone(59)

formed by further condensation of the active methyl group of (58) with excess benzaldehyde. Bergmann et al.[152] reported a second byproduct which has been shown by Pfleger and Plos[153] to be 4-benzylidene 1-carboxymethyl-2-styryl-5-imidazolone (60).



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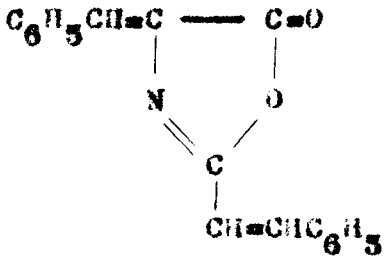

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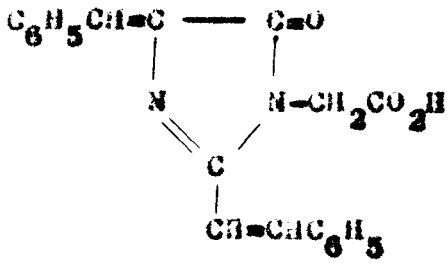
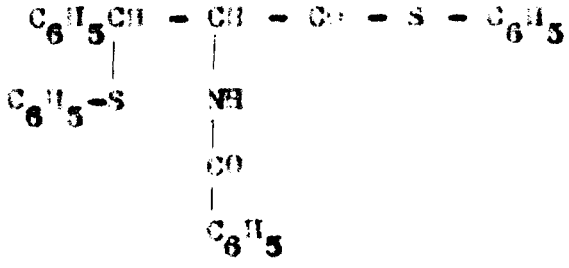


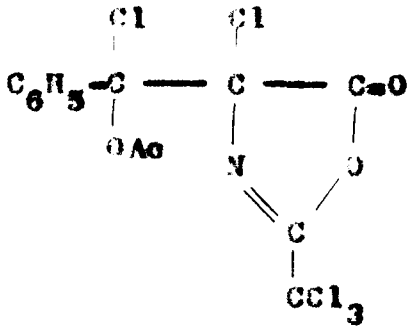
(60)

4-Arylidene-5-oxazolones undergo ring opening reaction with aromatic thiols and a second mole of thiol is then incorporated to give products such as (61)[154].



(61)

The chlorination of (58) in an acetic acid-acetic anhydride mixture leads to a pentachloroacetoxy compounds (62)[155] but in acetic anhydride only or in carbon tetrachloride, the dichloro analog (63) is obtained[156].



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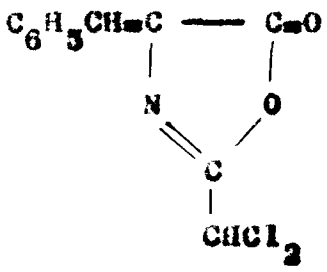
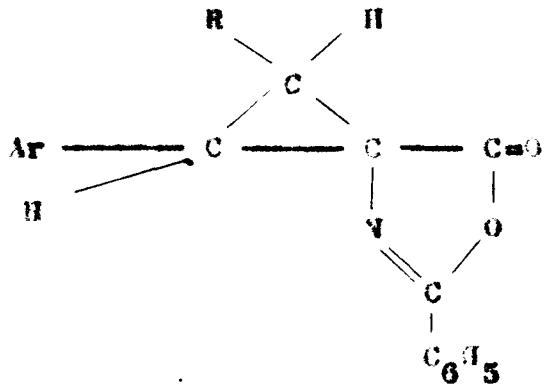


(63)

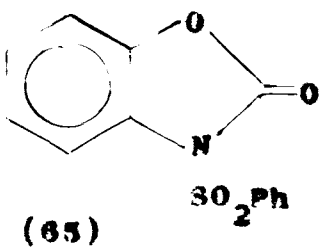
It has been shown[157] that 4-arylidene-2-phenyl-5-oxazolones react with diazoalkanes at exocyclic double bond to give compounds of type 64



(64)

R=H, CH_3

The reaction of N-benzenesulfonyl benzoxazolone[158] (65) with primary amine gave 2-phenylsulfonamido)-phenylcarmates (66, R=H, R'=Me, Et, Pr, Bu or CH_2Ph; NRR' = piperazino or morpholino). Secondary amines Me_2NH and Et_2NH reacted much more slowly and only 2-(phenylsulfonamido)-phenol was formed.



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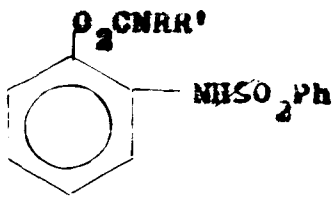


(66)

III. Reactions of Formic Acid

Formic acid is the strongest of the unsubstituted alkanoic monoacids. It has a pka of 3.77 as compared with 4.77 for acetic acid. Its relatively high acidity is due to the lack of alkyl groups and their attendants electron release by an inductive effect. This electron release causes deestabilisation of carboxylate anions resulting from ionization of the higher monocarboxylic acids.

1. Esterification

The high acidity of formic acid, makes use of mineral acid catalyst necessary, for esterification of many alcohols(68).

$$\underset{(67)}{HCOOH} + \underset{(68)}{ROH} \longrightarrow \underset{(69)}{HCOOR}$$

Complete esterification of primary, secondary and tertiary alcohols have been reported[159-160] the rate of esterification in neat formic acid was found to be 15,000-20,000 times that in neat acetic acid[159]. Formic acid reacts at room temperature with mercaptans (70) to yield trithioorthoformates(71)[161].

$$\underset{(67)}{HCOOH} + \underset{(70)}{RSH} \longrightarrow \underset{(71)}{HC(SR)_3}$$

Formic acid will also undergo trans esterification reaction such as that used to prepare anhydrous acrylic acid(72).[162]

$$HCOOH + CH_2=CHCOOCH_3 \longrightarrow CH_2=CHCOOH + HCOOH$$

(67) (72) (69)

2. Amidation and Related Reactions

Because of the acidity of formic acid, formylation of most amines occurs readily to yield the expected derivative (73).

$$R_2-\overset{R_1}{\underset{|}{N}}-CHO$$

(73)

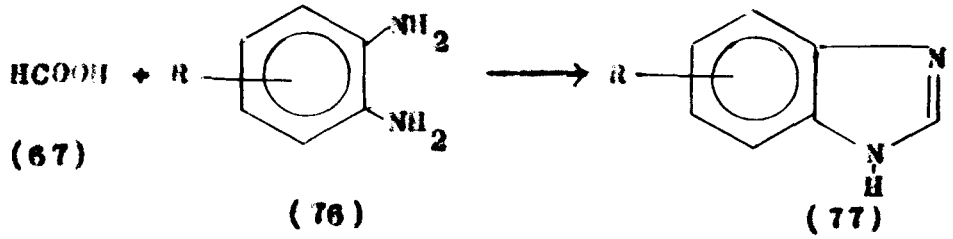
For example in the way N-methyl formanilide (73) ($R_1=CH_3$, $R_2=C_6H_5$) is prepared in 93-97 percent yield[163]. Transamidation also occurs with formic acid. ϵ-Caprolactam (74) and formic acid yield 7-formylamino caproic acid (75)[164].

$$HCOOH + \text{(74)} \longrightarrow HCONH(CH_2)_6COOH$$

(67) (75)

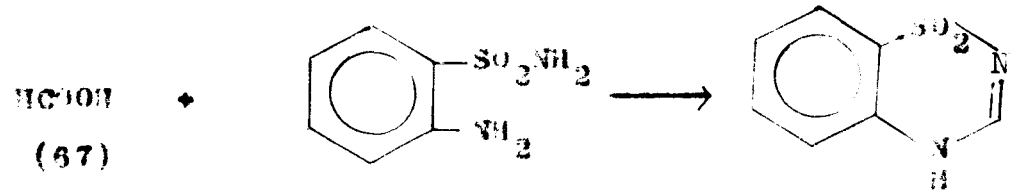
Reaction of diamines with formic acid lead to the formation of imide derivatives. These transformations are of use in the synthesis of heterocyclic compounds, 1,2-Diamino benzene (76)

in excellent yield by refluxing the two components[165,166]. The intermediate imide is hydrogenated by excess of formic acid.



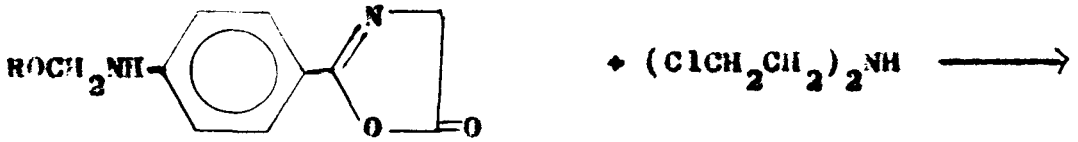
(67) (76) (77)

Similarly the reaction of o-sulphonamidoaniline derivative (78) with formic acid affords a synthetic pathway to 1,1-dioxo-benzothiadiazine (79)[167].

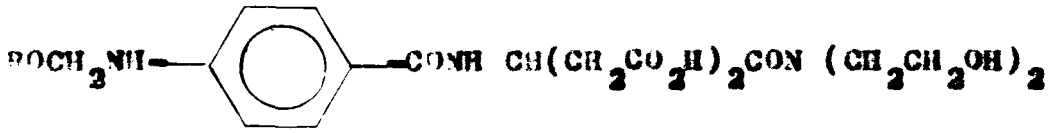


(67) (78) (79)

Oxazoline (80) reacted with $(ClCH_2CH_2)_2NH$ to give the DL-aspartic acid amides (81, R=H, Me, $ClCH_2$) which are useful as antitumour reagent[168].



(80)



(81)

3. Addition to Olefin

Formic acid will undergo Markovnikov addition to olefin (82) to yield formate esters (83) with greater ease than its homologs. The uncatalysed addition of 99-100 percent formic acid to oleic acid is nearly instantaneous, while acetic acid undergoes negligible addition[169].

(67) (82) (83)

Excellent yields are usually obtained in the absence of acidic catalyst. Indeed the uncatalysed addition of formic acid has been used as a quantitative method for the determination of dicyclopentadiene[170].

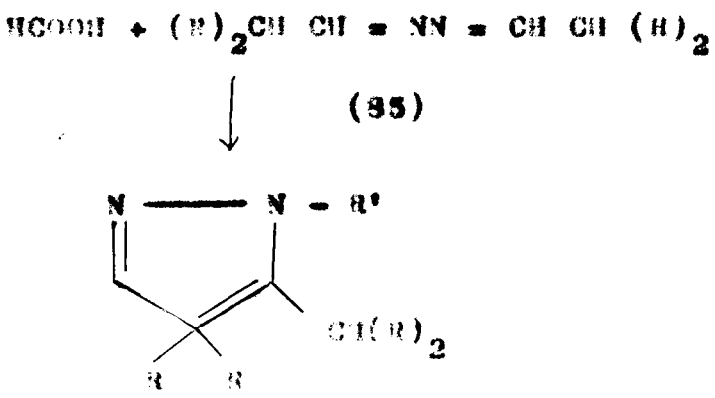
Acetylene react with formic acid in vapour phase to yield vinyl formate (84)[171]. Although this reaction proceeds readily, another report states that at reflux temperature formic

(67) (84)

acid does not add to a series of propargyl compound or 1,4-butyne diol[172]. Olefine and acetylene can also be reduced by formic acid in the presence of transition metal complexes[173].

4. Cyclization of Aldazines

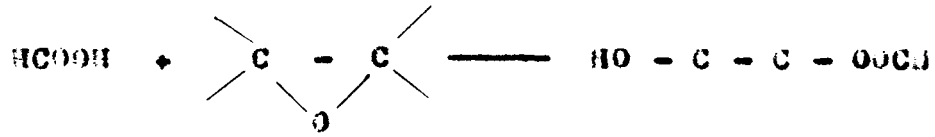
Anhydrous formic acid cyclises aldazine (85) to N-formyl-pyrazoline (86, R'=CHO) in good yield[174], these are readily hydrolysed to pyrazoline (86, R'=H).



(86)

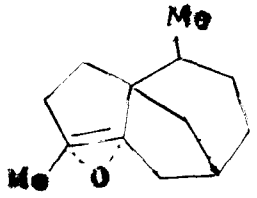
5. Reaction with Epoxide

The reaction of epoxide and formic acid is generally not a synthetically useful reaction though reaction is rapid the expected glycol monoformate (87) are accompanied by rearranged materials i.e. ketones, ethers and unsaturated compounds[175].



(87)

Reaction of cyperene epoxide (88)[176] with formic acid gave 30 percent of the alcohol (89) and 20 percent of the diol (90). Alcohol was formed by an allylic rearrangement.



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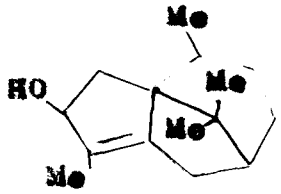

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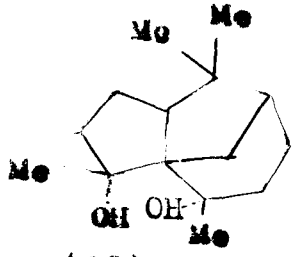


(90)

6. Beckmann Rearrangement and Related Reactions

Formic acid is useful reagent for effecting the Beckmann rearrangement of aromatic ketoximes to amides[177-179]. In 1926 it was reported that tertiary etaynylcarbanols (91) on treatment with formic acid are isomerized to unsaturated compounds[180]. Unsaturated aldehydes were then believed to be the product[150,151]. However subsequent work has shown that the main product are unsaturated ketones (92)[182]. Although the unsaturated aldehyde (93) are formed in smaller amount[183] and on occasion in appreciable quantities[184,185].

$$HCOOH + RCH_2-\underset{\displaystyle R'}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-C\equiv CH \longrightarrow$$

(67) (91)

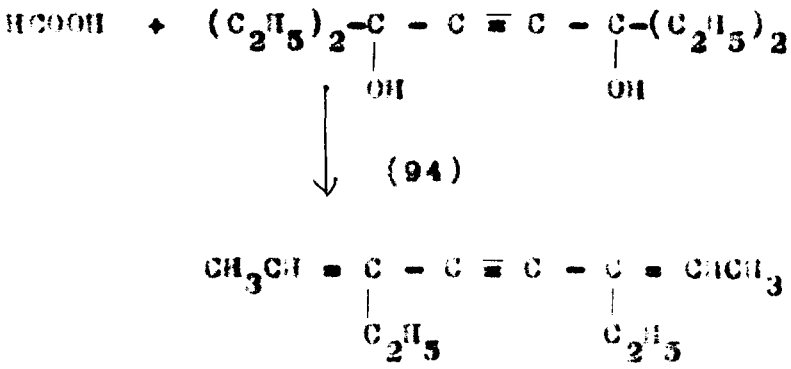
$$RCH=\underset{\displaystyle R'}{\overset{\displaystyle COCH_3}{\overset{|}{\underset{|}{C}}}} \quad + \quad RCH_2\underset{\displaystyle R'}{\overset{}{\underset{|}{C}}}=CHCHO$$

(93) (93)

Secondary acetylenic carbenol (91, R'=H) lose acetylene yielding an aldehyde which undergoes an acid-catalysed aldol reaction[186].

7. Dehydration

Formic acid brings about dehydration in many instances. For example refluxing it with diol 94 yield 95[187].



(94)

(95)

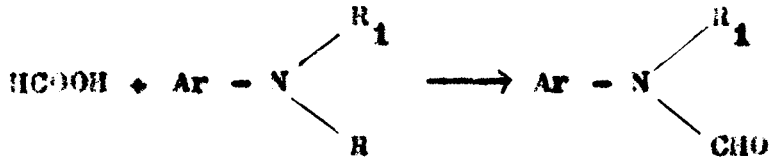
9. Autoprotolysis

Formic acid has a large autoprotolysis constant that is the equilibrium constant for formation of 96[188].

(96)

The protonated species 96 apparently takes part in several reactions. Treatment of aromatic tertiaryamine with azeotropes

of amine and formic acid causes dealkylation(generally less than 50 percent yield) as illustrated with general structure 97. Reaction of 96 and 97 loading to 98 is postulated. This then dissociated to the alcohol 68 and the protonated form of 97. This mechanistic proposal is constant with the effect of substituent on the aromatic ring and the basicities of the tertiary amines.



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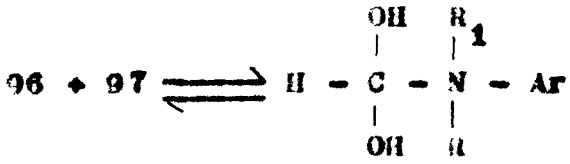

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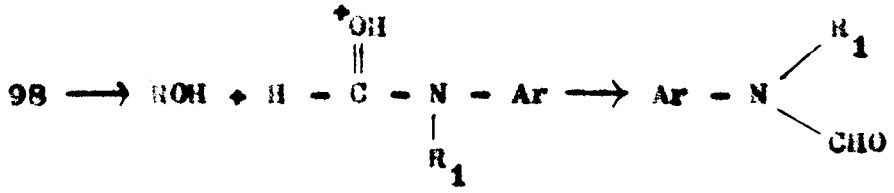
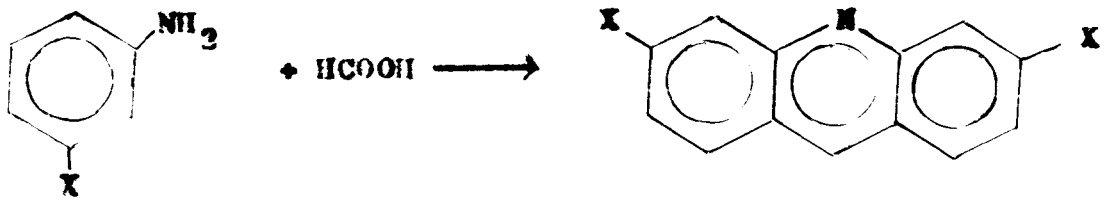


Species 96 may be envisioned as participant in the synthesis of acridines (100) from formic acid and m-hydroxy - or m-amino aniline (99) in the presence of hydrochloric acid[190,191].



(X=Oh, NH_2)

9. Reaction with Grignard Reagents

Reaction of Grignard reagent (101) with anhydrous formic acid gives low yields of aldehyde[192-193] presumably by way of intermediate 101a. Reaction of copper formate also gives low yield of (102)[192].

$$R'Mg\ X + HCOOH \longrightarrow X\ MgOOCH \xrightarrow{94}$$

(101)

$$\left[X\ MgO\underset{\displaystyle R'}{\overset{\displaystyle O\ MgX}{\underset{|}{\overset{|}{CH}}}}\right] \longrightarrow R'CHO$$

(101a) (102)

10. Reaction with Hydrogen Peroxide

Performic acid (103) result from treatment of formic acid with hydrogen peroxide via displacement of water from protonated hydrogen peroxide by formate ion.

$$HCOOH + H_2O_2 \longrightarrow H_2O + HCOOOH$$

(103)

This reaction is acid catalysed. Performic acid has been obtained in 90 percent purity[199], but owing to its instability, is usually not isolated. It has been used for preparation of glycol formate (87) for olefins[195,196].

$$\diagdown C = C \diagup + HCOOOH \longrightarrow HO - \underset{|}{\overset{|}{C}} - \underset{|}{\overset{|}{C}} - OOCH$$

(87)

This reaction involved formation of an intermediate epoxide which when attacked by formic acid over-all trans addition of peracid occurs.

11. Decomposition Reactions

(a) Formation of Carbon Dioxide and Hydrogen

Formic acid decomposes to carbon dioxide and hydrogen over a copper oxide-chromium oxide catalyst at 160-180°[197] or a platinum, iridium, rubidium palladium or osmium surface in the presence of oxygen at 150°[198]. A wide variety of other metallic compounds bring about this decomposition[199]. The reduction of olefinic bonds and of acids to aldehydes by formic acid at high temperature and pressure occurred[200]. Salicylaldehyde (among others) has reportedly been prepared in 92 percent yield in this way from salicylic acid over titanium dioxide[201]. The validity of this particular piece of work has been challenged, however[202] in view of this the general applicability of this procedure for the reduction of acids to aldehyde is questionable. The reduction of nitro compound to amines by carbon monoxide and water in alkaline medium[203] may involve formation of formate followed by evolution of carbon dioxide and hydrogen, the active reducing species. Aromatic ketones are reduced to hydrocarbon and aldehydes and aliphatic ketones to alcohols in this way[204,205].

Electrolysis of formic acid gives rise to carbon dioxide and hydrogen without peroxide formation[207]. However, an earlier publication describes formyl peroxide as an intermediate in the formation of carbon dioxide and formaldehyde[208]. Hydrogen and carbon dioxide would seem to arise via a bimolecular reaction of of formate ions[209] and also by way of bimolecular reaction of formate ion and formic acid[210]. Raney nickel catalyzes the decomposition of formic acid and formate ion at ordinary temperature. Thus by carrying out a reduction with Raney nickel in formic acid the hydrogen on the catalyst in constantly replenished. Using this technique olefins, ketones[211] and aldehyde[212] have been reduced. Raney nickel has also been used to catalyse the reduction of imines[213-214].

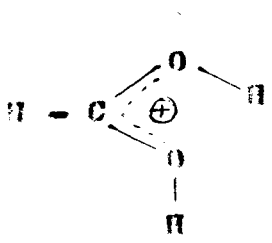
(b) Formation of Carbon Monoxide and water

Generation of high purity (99.9%) carbon monoxide from formic acid can be achieved by the use of sulphuric acid,[215] other mineral acid can also be used.[216-219] The reaction mechanism is involved protonation of the formic acid giving 96 followed by loss of water. This generates an incipient highly unstable

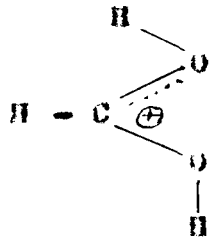
$$HCOOH + H^+ \longrightarrow 96 \longrightarrow H_2O + HCO^+ \longrightarrow CO + H^+$$

formylium ion (protonated carbon monoxide) which readily gives up a proton[220].

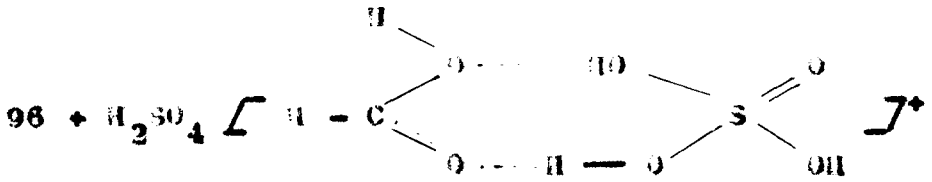
The recent p.m.r. study of formic acid in the system hydrofluoric acid antimony pentachloride at 67° revealed the presence of 96 in two distinct planar conformation 96a and 96b in a 77:23 ratio respectively[221]. No protonated carbon monoxide could be detected. The surprising lack of dehydration in these strong acids was alleged to their inability to hydrogen bond with 96 as is possible with sulphuric acid.

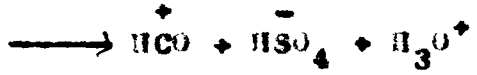


(96a)



(96b)





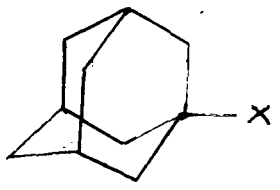
In the system sulphur dioxide fluorosulphuric acid antimony pentafluoride at -60°, 96a and 96b are present in nearly equal amount, acetic acid by contrast exists in cisoid form analogous to 96a to an extent of about 97 percent presumably due to steric effect of methyl group[222]. Chlorosulfonic acid

($ClSO_3H$) causes decomposition of formic acid to carbon monoxide and hydrogen chloride[223]. This is a convenient method of preparing the equimole mixture of these gases required in the Gatterman-Koch reaction for preparation of aldehydes.

Reaction of formic acid and an olefin (82) in the presence of sulphuric acid or hydrochloric acid result in formation of acid 104. This is known as the Koch reaction and has been thoroughly reviewed[224]. It involves formation of incipient carbon monoxide, since a carbonium ion is formed rearrangement often occurs, resulting in a mixture of carboxylic acids. Compounds which are precursors of olefins can also be carboxylated

$$\underset{(67)}{HCOOH} + \underset{(82)}{>C{=}C<} \xrightarrow{H_2SO_4} \underset{(104)}{HC(-)-C(-)-COOH}$$

in this way. Among this class are alcohols[225] and alkylhalides[226]. Examples of these reactions are the production of adamantane-carboxylic acid (105 x=COOH) from either alcohol (105 x=OH) or the bromide (105 x=Br) in 96 percent yield[227].



(105)

In the presence of sulphuric acid and alcohol or olefin, hydrocarbon are carboxylated by formic acid. The reaction involves removal of a hydride ion from the hydrocarbon to form a carbonium ion. The product result from the most stable carbonium ion. Incipient carbon monoxide is also involved here. Rearrangements are common. In this way admantane (105, X=H) yields 90 percent admantane carboxylic acid (105 X = COOH)[228,229], this reaction has already been discussed[230]. Carbon monoxide and water result from contact of formic acid and metallic compound at elevated temperature[199,231]. It has been suggested that carbon monoxide and water result from a secondary reaction of carbon monoxide and hydrogen once formed and that at high temperatures the secondary reaction is very fast, giving the impression of a direct reaction second order in formic acid[232]. This suggestion would also readily account for the co-occurrance of both sets of products in many instances of thermal decomposition[199,233,234], but it seems likely that the mechanism is similar to that in photolysis[235,236].

(c) Formation of Formaldehyde

A third type of decomposition which occurs concomitantly is the autoreduction of formates or formic acid in the presence of metals. Formaldehyde is formed in low yield (25 percent or less)[234,237,239]. Formaldehyde may result from autoreduction or from a secondary reaction of the hydrogen and carbon monoxide

produced. Methanol is produced by further reduction of formaldehyde[199]. In addition to methane[234,238], acetone furfural derivatives and pyruvic acid are also formed.

12. Formic acid as Reducing agent

From the above discussion of decomposition reaction of formic acid one might have predicted that formic acid could serve as reducing agent in view of its propensity to lose both hydrogens and form carbon dioxide. Indeed formic acid per se has been used to reduce a wide variety of organic compounds.

(a) Reduction of Imines

Reduction of imines (Schiff bases) by formic acid has long been known. The Leuckart reaction is probably the best known example of reduction by formic acid. Primary amines (107) are prepared from ketone (106) ammonia and formic acid. The reaction was reviewed in 1949[240]. Formamides may be substituted

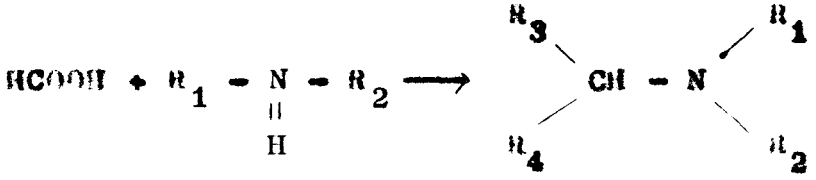
$$HCOOH + R_3 - \underset{\underset{O}{\|}}{C} - R_4 + NH_3 \longrightarrow R_3 - \underset{\underset{NH_2}{|}}{CH} - R_4$$

(106) (107)

for the formic acid-amine combination. In fact some authors have claimed, formamide is the active reagent in all these reactions[241-243]. However, since the reaction occurs below the

temperature necessary for formamide formation (150)[144] and different products have been observed with formamide and ammonium formate[245]. It appears that the ammonia gives rise to an imine which is reduced by formic acid to the amine (107)[246].

The Wallach reaction is an extension of Leukart reaction. Reaction of ketone (106) or aldehyde (106, R_3=H), formic acid and primary (108, R_2=H) or secondary amine (108) produces a secondary (109, R_2=H) or tertiary amine (101).



(108) (109)

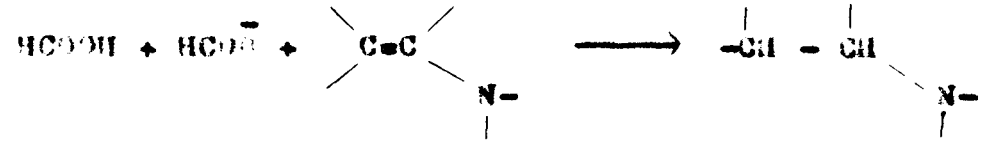
The mechanism again presumably involves reduction of an imine or in the case of secondary amine an enamine by formic acid or formate ion. This reaction has also been discussed as a modification of Leuckart reaction[240].

The Eschweiler-Clark methylation of amines with formaldehyde and formic acid[240], is but another example of the Wallach reaction. An N-methyleniminonium ion appears to be reduced by formate ions[246]. The reduction of imines per se by formic acid and formate ion is also known[244,247-250]. Hydrazones and azines are also reduced by formic acid and sodium formate to the corresponding hydrazines[251]. Probably as proposed[252,253] these reduction occur via the iminium ion (109) resulting from

protonation. Hydride transfer from formate ion would then yield the observed product , amine and carbon dioxide. One author however, favours a free radical pathway[254].

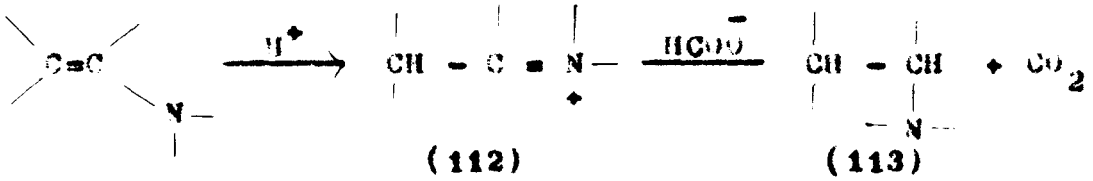
(b) Reduction of Enamines

Enamines (110) are reduced by formic acid[255] formate ion to saturated compound (III)[256-259]. The course of this reduction



(110) (111)

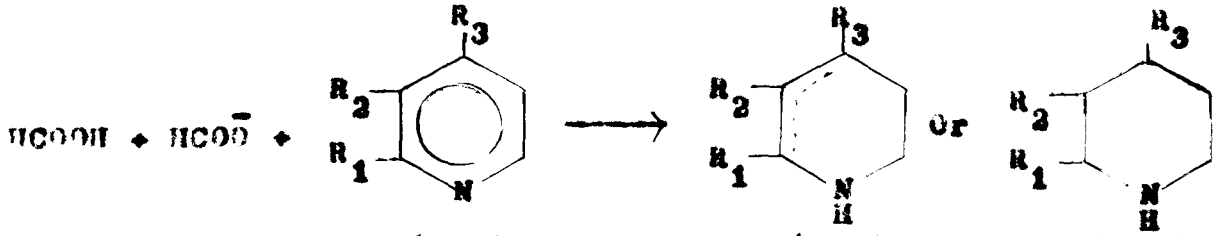
has been shown to include hydride transfer to the protonated enamine (112) by formate ion[259]. Deuterated formic acid was used for this study.



(112) (113)

This type of enamine reduction also undoubtedly occurs in the reduction of pyridine derivatives (113) to the piperidine (114) or tetrahydropyridine (114) compounds. The reduction of quinolines or isoquinoline (113, R_1, R_2 = benzo or R_2, R_3 = benzo respectively) leads to products of type 114[260,261]. Piperidine (115) results when a benzo group is not attached to the pyridine

nucleus[260,262-264]. An imminium type salt is formed by protonation. This is then reduced as a Schiff's base by formate ion to an enamine. Part of the hydride transfer occurs at the 4 position giving rise to two enamine function in one molecule. Both of these are reduced, the rest of the hydride is transferred to the 2 and 6 positions yielding a molecule containing a single

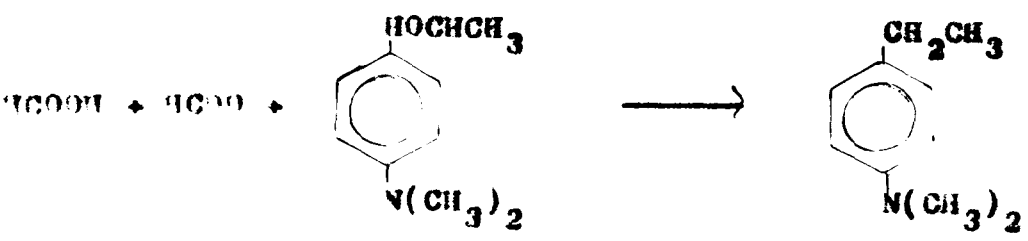


(113) (114) (115)

enamine function. This is reduced but the isolated double bond is not; so a mixture of tetrahydropyridine (114) and piperidine (115) result. The benzopyridines suffer reduction only to the tetrahydro state since further reduction would result in loss of resonance energy. Quaternized pyridine are similarly reduced[263].

(c) Reduction of Benzyl Alcohols and related compounds

Reduction of ∝-(p-dimethylaminophenyl)ethanol (116) to p-dimethylaminophenylethane (117) in 6 percent yield by formic acid and formate ion has been reported[244]. The reduction of triarylcarbinol (110, X=OH) has long been known. The corresponding



(116) (117)

hydrocarbons (118, X=H) result in generally quantitative yields[265-268]. It is also possible to reduce derivatives of triarylcarbinols to the hydrocarbons. Triarylmethylethyl ethers (118, X=OCH_2CH_3) and triarylcarbinyl chlorides (118, X=Cl) have

$$(Ar)_3 - C - X$$

(118)

been so reduced[269]. All of these reaction proceeded via formation of stable triaryl carbonium ion formates (119). Hydride transfer from formate ion to the carbonium ion forms the hydrocarbon and carbon dioxide[269-271] kinetics substantiate that prior ionization is necessary in view of the linear relationship between rate

$$HCOOH + Ar - \overset{Ar}{\underset{Ar}{C}} - X \longrightarrow (Ar)_3\overset{+}{C} - \overset{-}{O}OCH + H_2O$$

(119)

constants and ionization constants for the carbinols[272]. The slope indicates a half formed C-H bond in the transition state[272].

The silicon analogs the triarylsilanols (120, X=OH) are

$$HCOOH + Ar_3SiX \longrightarrow ArH$$

(120) (121)

also reduced by formic acid[273]. However, silanes (120, X=H) do not result. Rather, the main products are the arenes (121)

resulting from reductive cleavage of the aryl silicon bond. The chloride (120, Y=Cl) appears to be inert, but the silane (120, Y=H) undergoes cleavage to 121[273] implying that it may be an intermediate reaction.

Diols are easily converted into Lactones using formic acid along with inorganic acid[274].

(d) Reduction of Diarylmethanes

Refluxing pentamethylbenzene (122) and formaldehyde in formic acid solution for 1 hr leads to the formation of bis (pentamethylphenyl) methane (123) in good yield. Continued reflux leads to the formation of hexamethylbenzene (124) in 90 percent yield[275]. Attempts to bring about methylation on less heavily benzene lead only to Novalak and or Bakelite type products[276].

$$HCHO + HCOOH + C_6H(CH_3)_5 \longrightarrow C_6(CH_3)_5CH_2C_6(CH_3)_5$$

(122) (123)

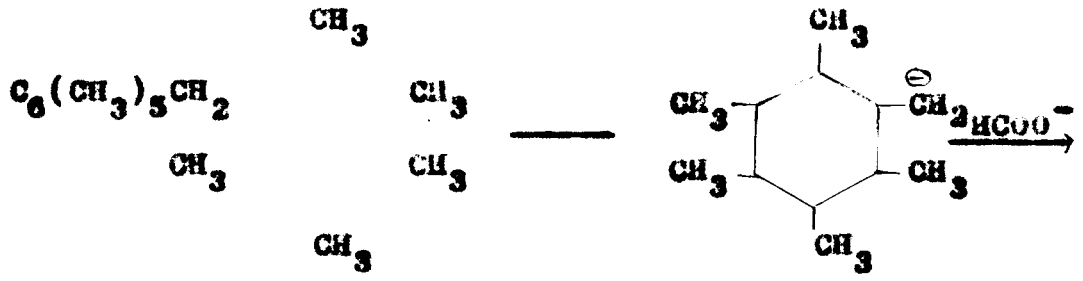
$$HCOOH + C_6(CH_3)_5CH_2C_6(CH_3)_5 \longrightarrow C_6(CH_3)_6$$

(123) (124)

A plausible mechanism might be protonation of the electron rich diarylmethane to give a structure such as 125 followed by loss of the pentamethylphenylcarbonium ion which could be reduced by formate ion to the observed product (124).

$$HCOOH + C_6(CH_3)_5CH_2C_6(CH_3)_5 \longrightarrow$$

(123)



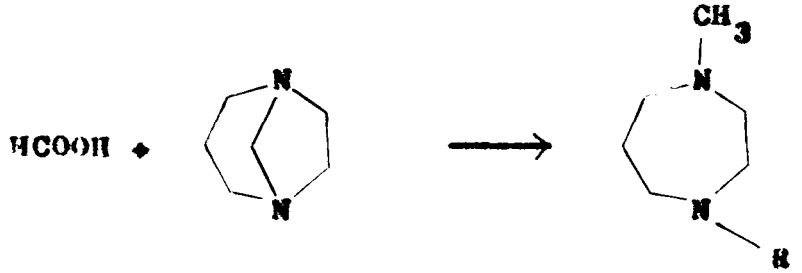
(125)

$$C_6(CH_3)_6 + CO_2$$

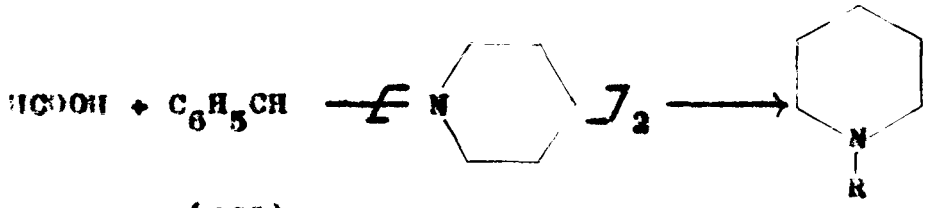
(124)

(e) Reduction of Diaminomethanes, Sulfonylaminomethane and Acylaminomethane

Diaminomethanes suffer reductive cleavage by formic acid to a monoaminomethane and formamide (via a primary or secondary amine) 1,3-Diazabicyclo [3.2.1] octane (126) is converted to 1-methyl-4-formylhomopiperazine (127, R=CHO) presumably via 127 (R=H)[377].



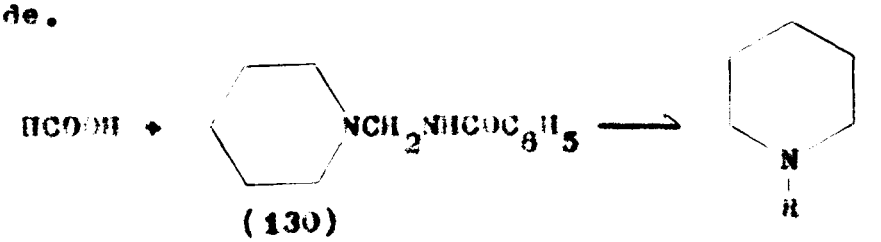
(126) (127)



(128) (129)

N,N'-Benzylidine bispiperidine (128) undergoes a similar reduction cleavage to N-benzylipiperidine (129, R=$CH_2C_6H_5$) and N-formylpiperidine (129, R=CH_3) by formic acid at room temperature[278].

Acylaminomethyl and sulfonylaminomethyl compounds undergo reduction fission by formic acid-tertiary amine azeotropes to yield unsubstituted amides or sulfonamides and the methyl compounds. For example N-benzamidomethylpiperidine (130) affords 97 percent of N-methylpiperidine (130, R=CH_3) along with benzamide.



(130)

R = CH_3

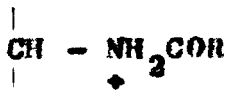
(129)

Reaction of these azeotropes and N,N'-benzylidinebisamides (131) yields acylbenzylamine (132) and amides(133).

$$HCOOH + HCOO^- + ArCH(NHCOR)_2 \longrightarrow ArCH_2NHCOR + H_2N\,COR$$

(131) (132)

These reactions most likely involve protonation of nitrogen. The protonated species (134) may then be reduced by formate ion by hydride transfer.



(134)

(f) Reduction of Inorganic Compounds

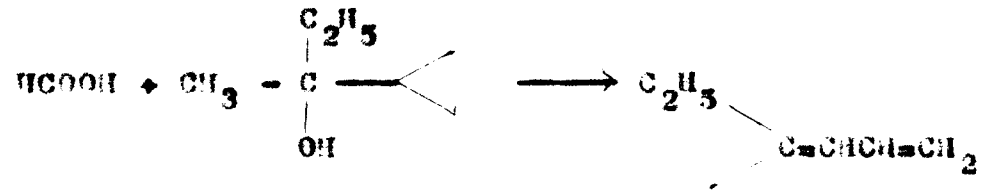
Reduction of some inorganic material (oxidising agent) by formic acid also occurs. Among the most significant of these are those involving sulfur compounds. The peroxydisulfate ($S_2O_8^{2-}$) reduction to sulfate (SO_4^{2-}) can be catalysed by silver ion[279]. Sulfur dioxide (SO_2) is reduced at 25° to thiosulfate ion ($S_2O_3^{2-}$) via the radical ion SO_2^- and hydrosulfite ion ($S_2O_4^{2-}$)[280]. The formic acid tertiary amine azeotropes will reduce sulfur dioxide to elemental sulfur in good yield at 100°[276].

The normal inorganic oxidising agents (dichromate, permanganate) are of course reduced by formic acid. The reduction of lead tetraacetate is the basis of a method for quantitative determination of formic acid[281-282].

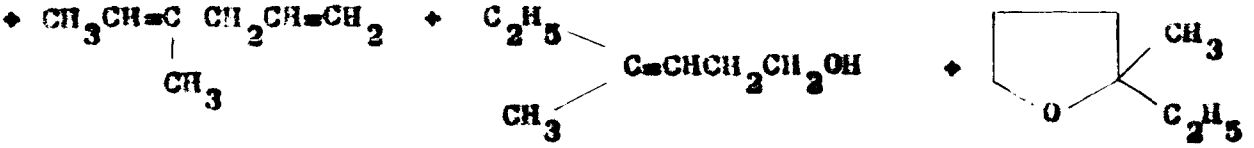
13. Solvolysis Reactions

Use of formic acid in solvolysis reactions has produced a massive volume of literature. Formolyses have been intimately involved in the nonclassical carbonium ion dialogue. Solvolysis reactions have been defined as those in which the solvent combines with the substrate[283].

Tertiary cyclopropylcarbinols undergo rearrangement when solvolysed. For example, methylethylcyclopropylcarbinol (135) produces olefins 136, 137 and 138 resulting from ring opening and furan 139 formed by ring opening and subsequent ring closure[284]. Similar compounds give like results[285-287].



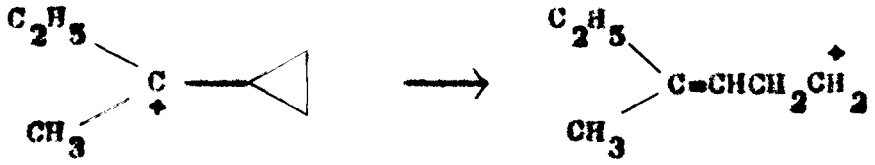
(135) (136)



(137) (138) (139)

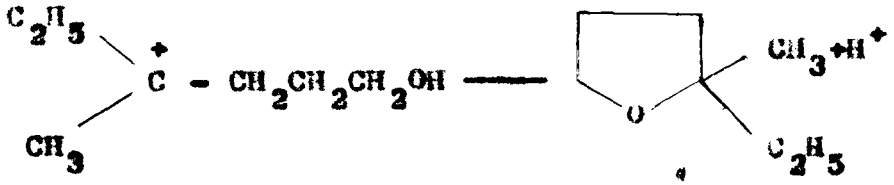
The formation of these compounds can be explained by the intermediacy of carbonium ion 140, which subsequently loses a proton to form the normal dehydration products. Rearrangement of 140

gives 141 which reacts with water to form 138 or lose a proton to give 136. Protonation of the double bond in 138 followed by



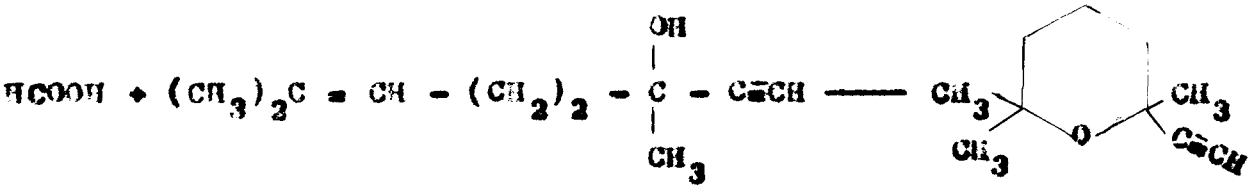
(140) (141)

intramolecular attack of the hydroxyl oxygen on the resultant carbonium ion (142) would give the protonated form of 139.



(142)

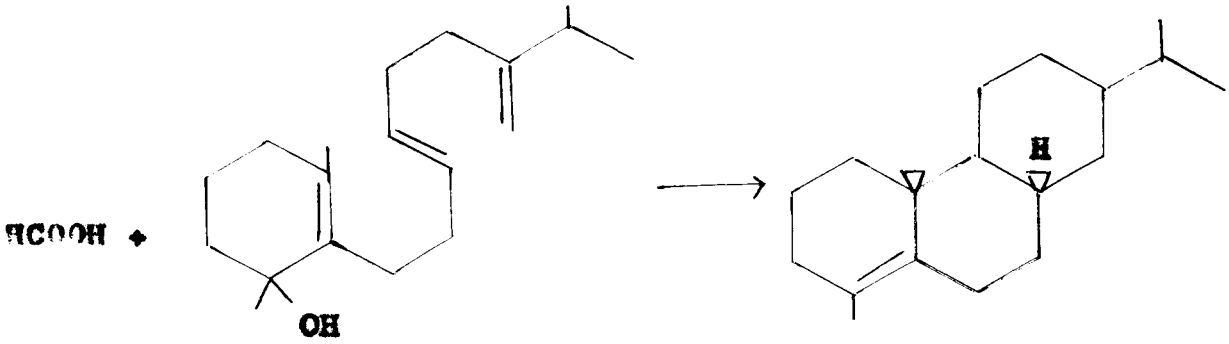
A reaction similar to the latter has been reported in the formation of 126 for dehydrolinalool (143) and formic acid[288].



(143) (144)

One of the most interesting uses of solvolytic reactions in terms of our understanding of stereochemistry of biosynthetic processes is the cyclization of complex polyolefins. An example of this is the conversion of 145 to 146 by treatment with formic acid at room temperature for 11 min[289]. The reaction probably proceeds

by way of the carbonium ion resulting in protonation of hydroxyl group and loss of water[290].



(145) (146)

Formolysis reactions have yielded information about the nucleophilicity and ionization power of formic acid. In nucleophilicity, formic acid appears to be less powerful than any of the commonly used solvent system[291]. However, formic acid is second only to water ionizing power i.e. the ability of a solvent to promote ionization of species by an SN^1 type[292,293] process. This property depends on solvent qualities to a greater extent than on dielectric constant[294]. The coupling of these two factors is responsible for the higher protonation of byproducts observed in formic acid solvolyses. Detailed discussion of formolytic reaction in general can be found in texts on the subject[283,295].

14. Free Radical Reactions

Very few authenticated example of free radical reactions of formic acid are known. This is due to the propensity for excited formic acid molecules to undergo single step molecular rearrangements to decomposition products without the intermediacy of free radicals[236,296].

Photolysis of formic acid has been reported to yield oxalic acid[297], but this has been disproven[236,298]. The formation of oxalic acid in low yield by photolysis of an aqueous formic acid - carbon dioxide solution has been reported, however[299]. Thus, if water is present photolysis could conceivably yield oxalic acid. The photolysis of water yields hydrogen atoms and hydroxy radicals. The former reacts with hydroxyl ion to form a solvated electron which can transform carbon dioxide to CO_2^- radical ion. Interaction of formate ion and hydrogen atom or hydroxy radical can also form this radical ion. The reaction of the radical ion with formate ion is a chain reaction which yields oxalate ion[299].

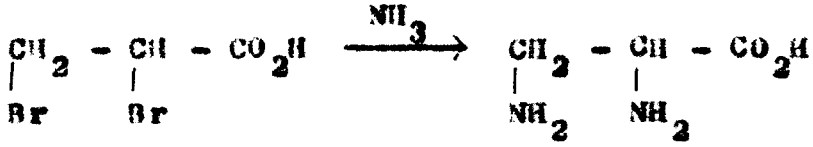
Metal formates are converted in good yields to oxalates by heating to 360-440°[300-308]. The reaction is possibly a free radical process occurring on metal atom[238].

Reaction of chlorine with formic acid in ultraviolet light gives rise to hydrogen chloride and carbon dioxide[309] possibly via unstable chloroformic acid[310].

Diamino Acids

1. Amination of α,β-dibromopropionic acid

β-Aminoalanine (148) was first prepared by the amination of α,β-dibromopropionic acid (147)[311-313].

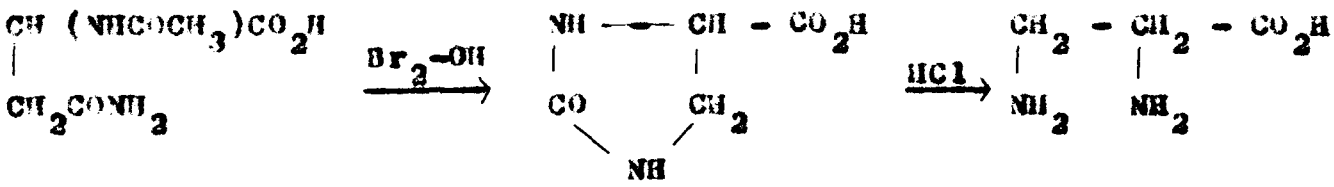


(147) (148)

A related synthesis of β-aminoalanine but of little practical value was employed using Serine as starting material[314].

2. Hofmann degradation Method

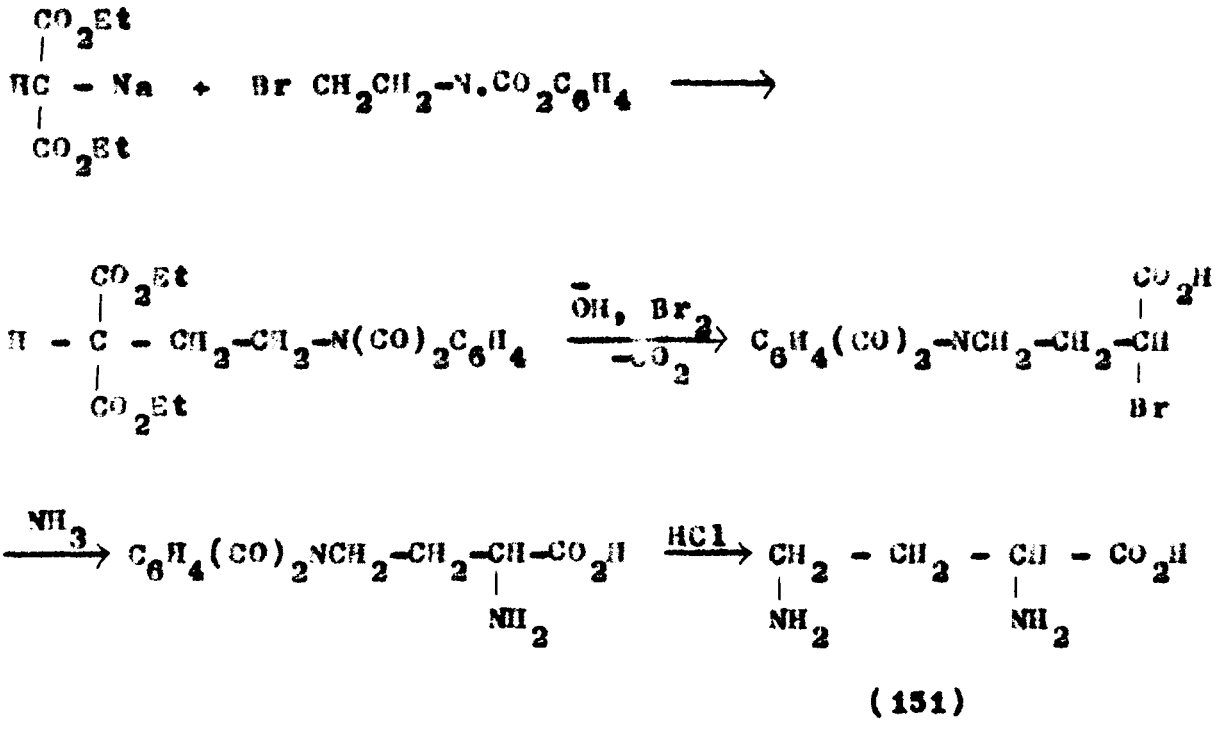
β-Amino-L-Alanine (150) was prepared from acetyl L-asparagine (149) by Hofmann degradation without loss in optical configuration.[315]



(149) (150)

3. Fischer Synthesis

Fischer[316] in 1901 prepared γ-aminobutyrine and ornithine by condensing sodium malonic ester and bromoethylphthalamide. Saponification of γ-phthalamidoethylmalonicethyl ester followed by bromination and then decarboxylation gave γ-phthalimido α-bromobutyric acid. This on amination and successive hydrolysis led to the isolation of γ-aminobutyrine (151).



(151)

This method has also been employed for the preparation of ornithine[317].

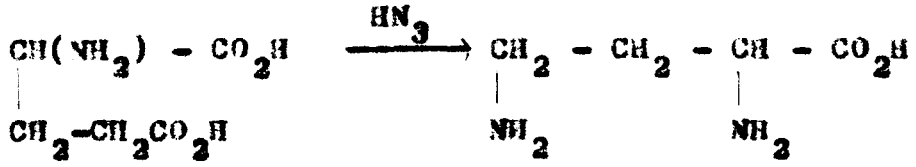
4. Synthesis of Amino Acids by Schmidt Method

The Schmidt's reaction has been applied to the synthesis of ornithine (152). Hydrazoic acid in chloroform was slowly added to a solution of ∝-aminoadipic acid in concentrated H_2SO_4 at 45°[318].

(152)

Another reactant with hydrazoic acid which was effective in yielding ornithine under the above conditions was 1:1:4 tricarboxybutane[319].

Rothchild and Fields[316] also prepared 1:1:3 tricarboxypropane which on treatment with hydrazoic acid yields γ-aminobutyrine.



5. Strecker type Synthesis

It was reported in 1928 by Keimastue and Sugasawa[320] that γ-benzoylaminobutyraldehyde is converted to cyanohydrin through cyanide and then with ammonia to the aminonitrile which is

directly benzoylated in the presence of pyridine. Heating with HCl gave ornithine.

$CH_2(NHCOC_6H_5)CH_2CH_2CHO \xrightarrow{KCN}$

$CH_2(NHCOC_6H_5)CH_2-CH_2CH(OHCN) \xrightarrow{NH_3} \xrightarrow[Pyridine]{C_6H_5COCl}$

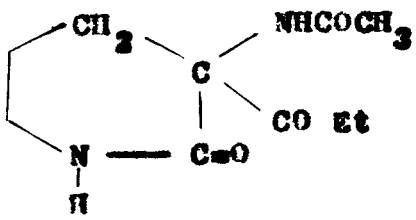
$CH_2(NHCOC_6H_5)CH_2CH_2CH(NHCOC_6H_5)CN \xrightarrow{HCl}$

$CH_2(NCOC_6H_5)CH_2CH_2CH(NH_2)CO_2H \longrightarrow CH_2(NH_2)CH_2CH_2CH(NH_2) - CO_2H$

(152)

Albertson and Archer in 1945 have given the simplest synthesis of ornithine. Acrylonitrile was treated with acetamedomalonate in presence of sodium ethoxide to yield ethyl α-acetamido α-carbethoxy γ-cynobutyrate which on catalytic hydrogenation gave -3-acetamido-3-carbethoxy piperidone. On hydrolysis ornithine was formed.

$CH_2{=}CHCN + HC(CO_2Et)_2 - NHCOCH_3 \xrightarrow{NaOEt} NC\,CH_2CH_2 - C(CO_2Et)_2 - NHCOCH_3 \xrightarrow{Ni/H_2}$



$\xrightarrow{HCl} CH_2(NH_2) - CH_2 - CH_2 - CH(NH_2) - CO_2H$

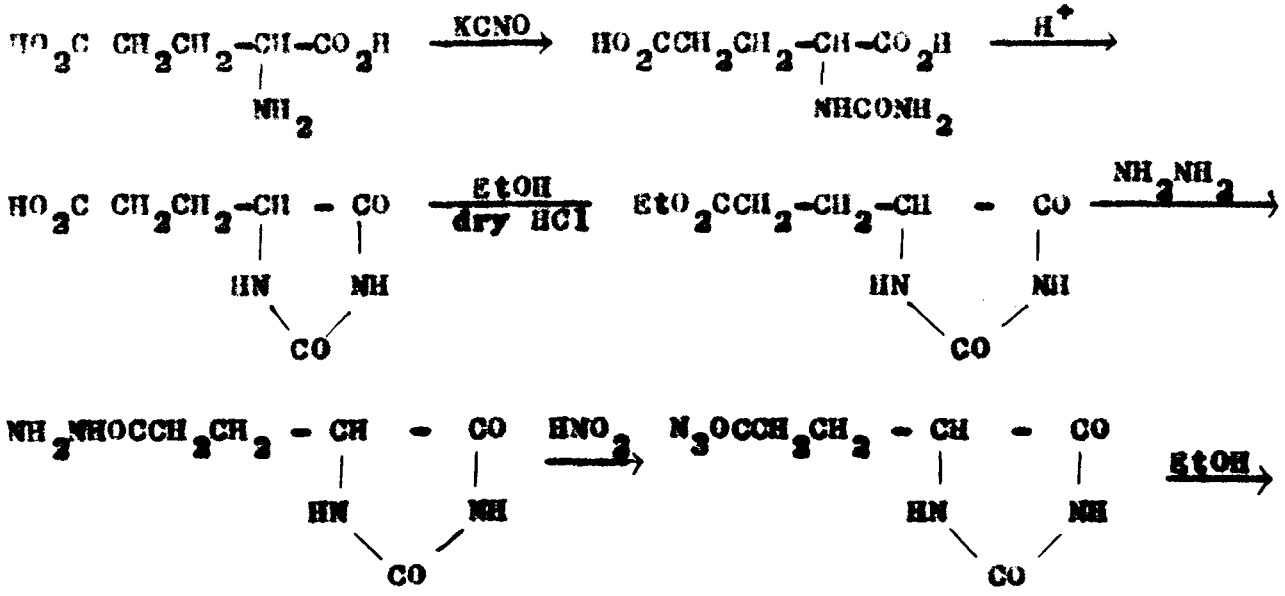
(152)

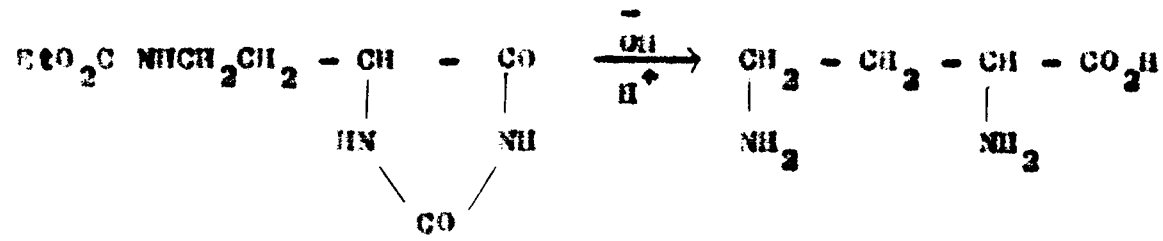
A somewhat similar procedure to obtain 3-acetamido-3-carbethoxy-piperidone was employed by Warner and Moe[321]. A more novel approach to reach the piperidone was described by Shapiro and Abramovitch[322].

Another procedure[323] involved condensation of acrylonitrile with diethylnitromalonate for the synthesis of ornithine.

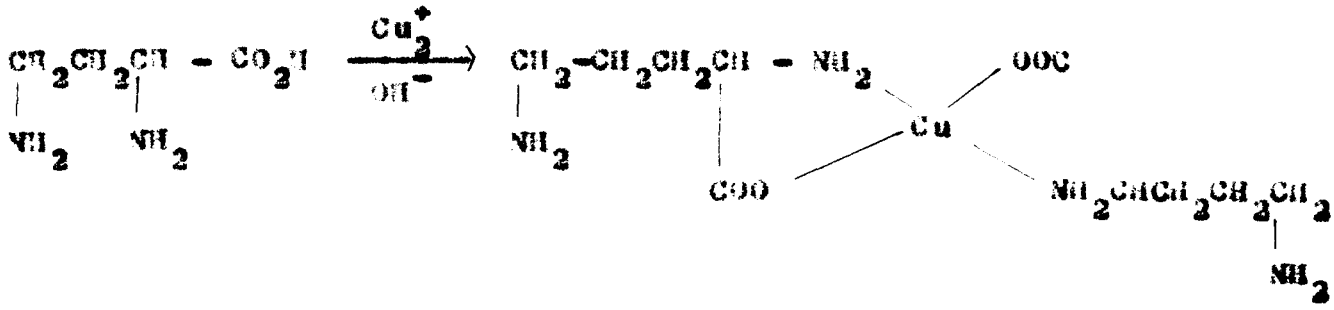
6. Miscellaneous Methods

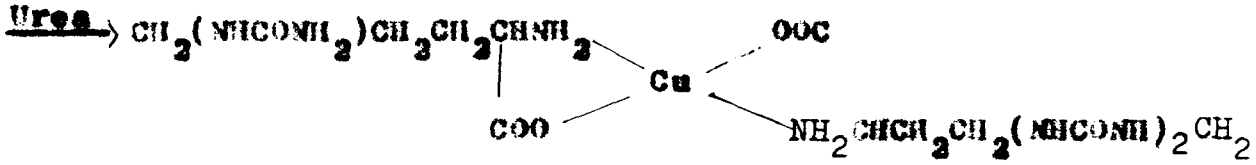
Akabori and Numano[324] used glutamic acid as starting material and converted it by reaction with cyanate to α-carbamylglutamic acid and then with acid to hydantoin propionic acid, this compound was esterified in ethanol-dry HCl and with nitrous acid. Treatment with ethanol at 40-60° yield corresponding urethane which on refluxing with barium hydroxide solution yielded γ-aminobutyrine.

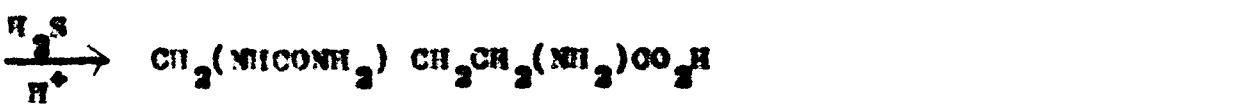




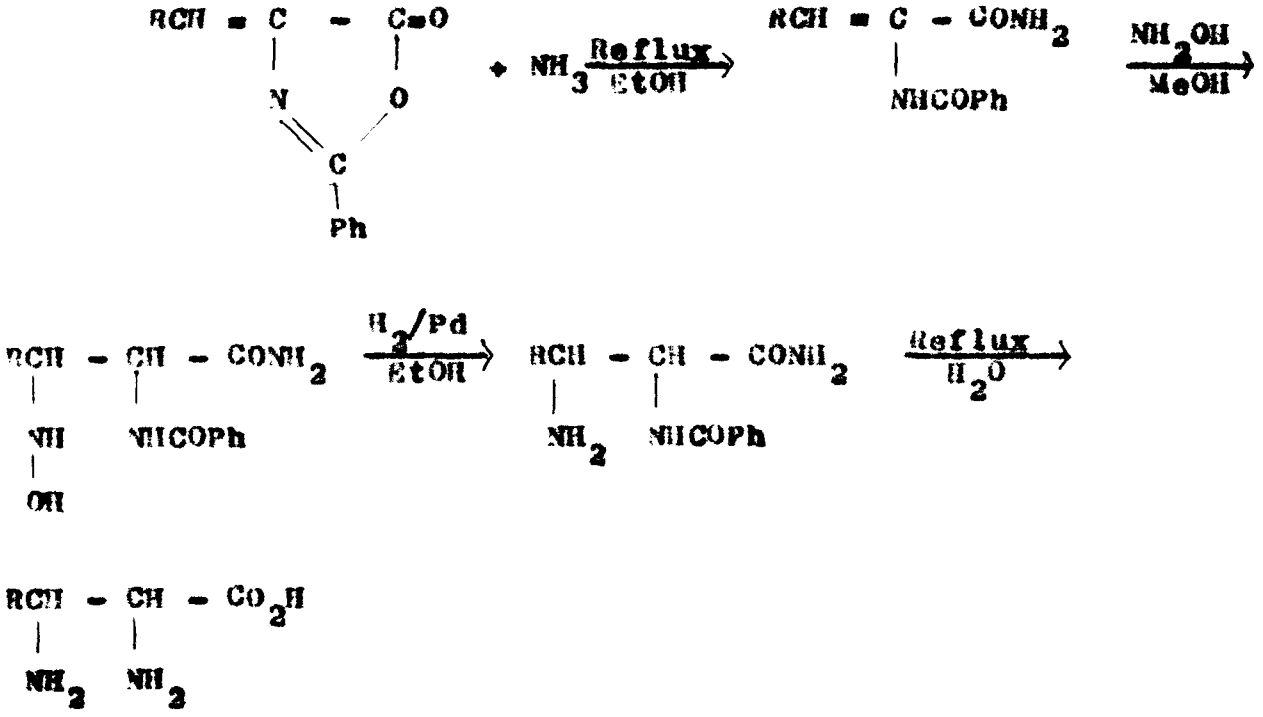
King and Kidd[325] obtained γ-aminobutyrine by the reaction of glutamic acid and phthalic anhydride. Gandry[326] used phthalic anhydride and 3-aminopropanol in the synthesis of ornithine. The first synthesis[327] of citrulline involves ornithine as starting material. A simpler method of blocking the α-amino group of ornithine was revised by Kurtz[328] and further elaborated in 1949[329] which consisted in forming the copper salt where in the α-amino group was chemically unreactive.







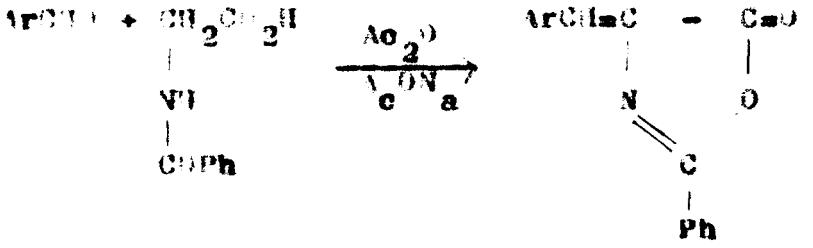
Recently[145] 2-phenyl-4-benzal-5-oxazolone was used for the synthesis of β-aminophenylalanine. This method was further modified[146] by ammonolysing azlactone to form α-N-benzoylamino-acrylic acid which was treated with hydroxylamine to give α-N-benzoylamino-β-hydroxylamino acid amide. This on reduction using palladium charcoal (10% Pd), gives α-N-benzoylamino-β-amino acid amide which on hydrolysis afforded α,β-diamine acids.



DISCUSSION

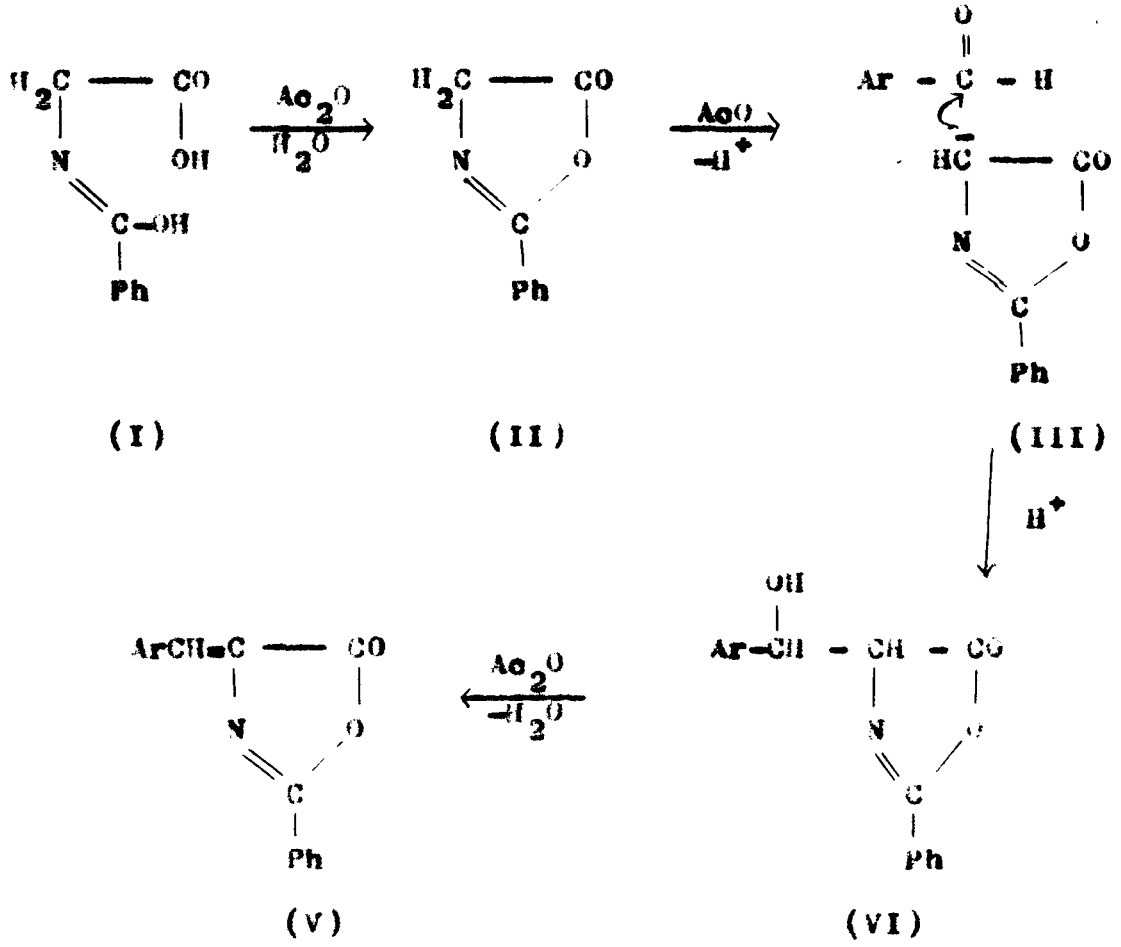
I. Preparation of Azlactones

Plochl[1] prepared the first unsaturated azlactone by the condensation of benzaldehyde with hippuric acid in presence of acetic anhydride. However, it remained for Erlenmeyer[2,3] to determine the structure of the product. The reaction of an aldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate is commonly referred as the Erlenmeyer Azlactone reaction (Loc Cit.).



The intermediate 2-phenyl-5-oxazolone (II), formed by the action of acetic anhydride on acylglycine (I), contains a methylene group which is doubly activated by the carbonyl group and the carbon nitrogen unsaturated double bond. Condensation takes place between the aldehyde and the azlactone (II) so formed, via (III), to yield 2-phenyl-4-(1'-hydroxybenzyl)-5-oxazolone (IV) which readily rearranges to 2-phenyl-4-benzylidene-5-oxazolone (V) by losing the hydroxyl group of the benzyl carbon

and proton of the methylene group in the form of a water molecule (Scheme 1).



Scheme 1

For the preparation of azlactone, we have tried a number of basic catalysts; i.e. sodium acetate, potassium carbonate, lead acetate and potassium bicarbonate. A brief account of the results obtained by us is given below.

Azlactones obtained from carbonyl compounds have been prepared by heating carbonyl compound, hippuric acid and freshly

fused sodium acetate with excess of acetic anhydride for varying length of time (15 min. -3 hrs). Table 1 shows the result obtained.

Table 1

Preparations of azlactone using sodium acetate

Carbonyl compounds	Reaction time	Yield %
1. Anisicaldehyde	30 min	80
2. Vanilline	15 min	75
3. Cinnamaldehyde	20 min	60
4. o-Methoxybenzaldehyde	30 min	75
5. p-Hydroxybenzaldehyde	10 min	90
6. p-Dimethylaminobenzaldehyde	20 min	69.2
7. Veratraldehyde	2 hr	71
8. β-Resorcylaldehyde	2 hr	91.2
9. Furfuraldehyde	10 min	48.3
10. 1-Naphthaldehyde	1 hr	62.8
11. Acetone	6 hr	39
12. Cyclohexanone	45 min	24.6

Glat[37] showed that potassium carbonate was an excellent catalyst for the condensation of aldehydes with hippuric acid and superior to sodium acetate. We used this catalyst in several preparation

and obtained excellent yields. In such cases a mixture of an aldehyde, hippuric acid and potassium carbonate is stirred with acetic anhydride at room temperature. The reaction mixture set into a paste. The condensation takes place without external heating and is complete in a shorter period of time with appreciably higher yield than those obtained by the standard method. Crotonaldehyde yield 31 % of the azlactone when we take anhydrous sodium acetate. The yield increased to 40 percent when potassium carbonate is employed as a catalyst. Table 2 gives the result obtained.

Table 2

Preparation of azlactone using potassium carbonate

Aldehyde	Yield %
1. Benzaldehyde	62
2. Salicylaldehyde	71
3. Crotonaldehyde	40

Finar and Libermam[101] reported the conditions under which aliphatic aldehydes were used in the Erlenmeyer azlactone synthesis[12-14], and showed that much improved yield of the azlactones were obtained with lead acetate as catalyst.

When cyclic ketones are used in this reaction the yields are much lower (8-10%).

We have also used potassium bicarbonate as a catalyst. Condensation takes place similarly as in the case of potassium carbonate. The pure products are obtained directly in higher yields. The use of potassium bicarbonate permitted the reaction to occur at room temperature. Carter[330] reported 67 percent yield of the piperonal azlactone. We prepared this azlactone in 82 percent yield by replacing the usual catalyst sodium acetate by potassium bicarbonate. The yield of crotonaldehyde azlactone remains unchanged with this catalyst (Table 3).

Table 3

Preparation of azlactone using potassium bicarbonate

Aldehydes	Yield %
1. Piperonal	82
2. Crotonaldehyde	40
3. Indolyl-3-aldehyde	90

Azlactones have usually been isolated either by cooling the reaction mixture and removing the azlactone by filtration or by pouring the cold reaction mixture into ethanol or water. Thus, allowing excess of acetic anhydride to decompose and

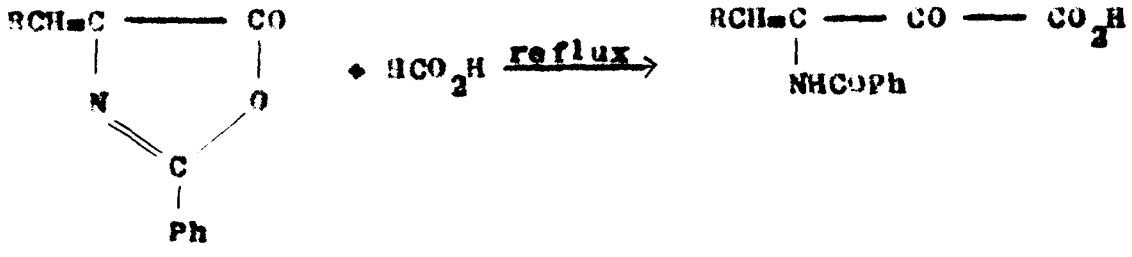
collecting the azlactone. In case of cyclohexanone the azlactone has been extracted with boiling light petroleum-ether (b.p. 40-60) after decomposition of acetic anhydride with water.

Most of the azlactones have been purified by recrystallization from ethanol. Chloroform and ethanol are employed for the recrystallization of azlactone of cinnamaldehyde. The azlactone prepared from p-dimethylaminobenzaldehyde is recrystallized from benzene. The azlactone of vanillin is purified by recrystallization from glacial acetic acid.

II. Synthesis of 3-Substituted Pyruvic acids

(1) Formic acid process

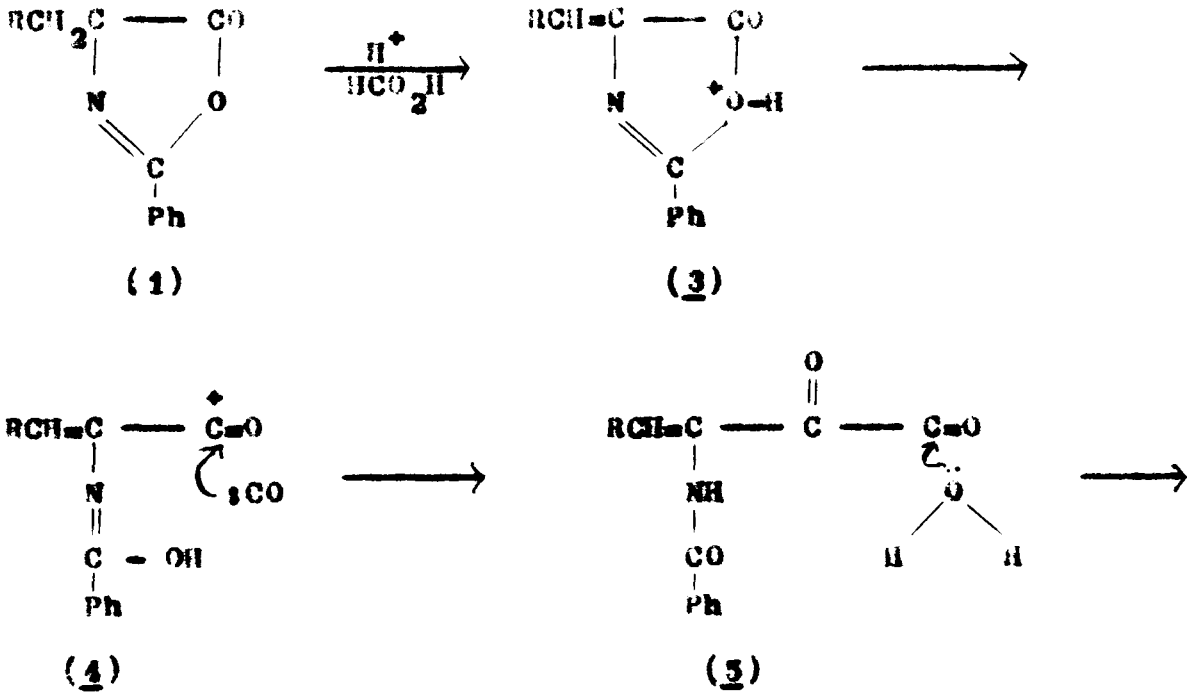
Azlactones, both saturated and unsaturated react with anhydrous formic acid forming 3-substituted pyruvic acids (2). The chemistry discussed in this reaction involves an interesting feature.



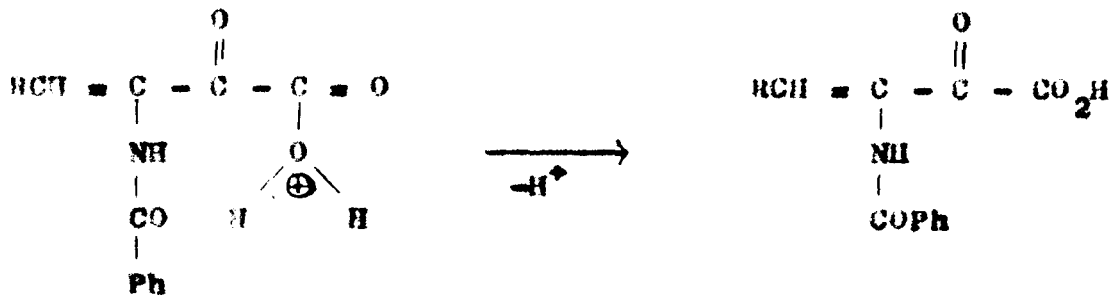
(1) (2)

(n-C_6H_5, p-$CH_3OC_6H_4$, $C_6H_5CH{=}CH$, o-OH-C_6H_4, p-OH-C_6H_4, p-$(CH_3)_2N$-C_6H_3, 3,4-$(OCH_3)_2C_6H_3$, 3,4-OCH_2O-C_6H_3, o-$CH_3OC_6H_4$, C_9H_6N, C_4H_3O, $(OH)_2C_6H_3$, $(CH_3)_2$-, C_6H_{10}, $C_{10}H_7$, $OH(C_6H_3)OCH_3$, $CH_3CH{=}CH$).

The proposed mechanism for this unusual reaction is depicted in Scheme 1. When the reaction of formic acid with azlactones is carried out protonation of oxygen atom of oxazolone ring takes place (3) and subsequently the ring is opened forming a positively charged species 4. This reacts with carbon monoxide, formed during the course of reaction, to yield another intermediate 5. Water molecule is added to it giving hydronium ion 6. A proton is eliminated from 6 resulting in the formation of keto acid 2. Hartenstein and Fridovich[331] reported that CO and H_2O, necessary for such reactions, must have been provided by the decomposition of initially dry formic acid. Since formic acid is stable under these conditions, one must conclude that



(1) (3) (4) (5)



(6) (2)

Scheme I

azlactone somehow catalyzes the decomposition of formic acid (Table 4).

IR spectra shows characteristic bands in the region 1695-1795 cm^{-1} assigned to CO stretching mode of a α-keto acid. Bands appeared at 3150-3300 cm^{-1} are due to NH stretching.

NMR spectra (CCl_4) indicated proton signals of COOH in 2 appeared at 9.2 - 9.7 δ and of NH at 8.2 - 8.9 δ. The proton signals of HC = C- is found to be at 6.0 - 6.9 δ.

(11) Cyanide Process

Several preparative methods for the 3-substituted pyruvic acids consist in the reaction of N-benzoylaminoacrylic acid 7 with an equivalent amount of phosphorous pentachloride to afford N-benzoylaminoacryloyl chloride 8. On treatment of chloride 8 with potassium cyanide, we obtain N-benzoylaminoacrylic acid cyanides 9 which on hydrolysis produce the target keto acids 2.

Table 4

Synthesis of 3-Substituted Pyruvic acids (2)

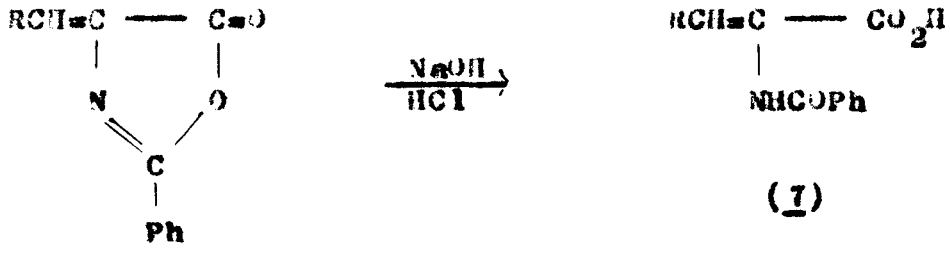
S. No.	Compounds*	Formic Acid Process		Cyanide Process	
		M.P. °C	Yield %	M.P. °C	Yield %
1.	3-N-Benzoylamino-3-(p-methoxybenzal)pyruvic acid	206	72	206	48
2.	3-N-Benzoylamino-3-(3'-methoxy-4'-hydroxybenzal)pyruvic acid	178	70	178	43
3.	3-N-Benzoylamino-3-cinnamylidene pyruvic acid	225	65	225	39
4.	3-N-Benzoylamino-3-(o-methoxybenzal)pyruvic acid	201	85	201-202	54
5.	3-N-Benzoylamino-3-(p-hydroxybenzal)pyruvic acid	220	60	220	36
6.	3-N-Benzoylamino-3-(p-dimethylaminobenzal)pyruvic acid	158	58	158	38
7.	3-N-Benzoylamino-3-(3',4'-dimethoxybenzal)pyruvic acid	190	95	190	64
8.	3-N-Benzoylamino-3-(2',4'-dihydroxybenzal)pyruvic acid	160	68	160	44
9.	3-N-Benzoylamino-3-furfurylidenepyruvic acid	210	84	210	57
10.	3-N-Benzoylamino-3-(1'-napthylidene)pyruvic acid	218	64	217-18	42
11.	3-N-Benzoylamino-3-isopropylidene pyruvic acid	126	62	126	36
12.	3-N-Benzoylamino-3-cyclohexylidenepyruvic acid	188	56	188	30
13.	3-N-Benzoylamino-3-benzalpyruvic acid	252	95	251-52	62
14.	3-N-Benzoylamino-3-(o-hydroxybenzal)pyruvic acid	115	60	114-15	36
15.	3-N-Benzoylamino-3-crotonylidenepyruvic acid	182	68	182	34
16.	3-N-Benzoylamino-3-piperonylidenepyruvic acid	179	94	179	60
17.	3-N-Benzoylamino-3-indolylidenepyruvic acid	240	88	240	52

*Compounds reported for the first time.

The chief drawback of the procedure outlined is the sequence of reaction leading to keto acid from azlactone, generally involving four steps and isolation of intermediate at each step results in lower yields of keto acids, conversion of acid chloride to acid cyanide requires longer time and above all, phosphorous pentachloride and potassium cyanide are inconvenient to handle.

(a) Treatment of azlactones with sodium hydroxide Synthesis of N-Benzoylaminoacrylic acids

Azlactones can be hydrolysed to corresponding acids using alkali[12] or acid[38]. Azlactones are heated under reflux with sodium hydroxide, after cooling the solution is acidified to congo red with hydrochloric acid. Bright crystals of N-benzoylaminoacrylic acids 7 are obtained (Table 5).



(7)

(b) Treatment of N-benzoylaminoacrylic acids with Phosphorous pentachloride. Synthesis of N-benzoylaminoacryloyl chlorides

The acids can be converted to acid chlorides using phosphorous pentachloride[332]. A mixture of N-benzoylaminoacrylic acid and phosphorous pentachloride in equimolecular proportion on

Table 5

Synthesis of N-Benzoylaminoacrylic acids (7)

No.	N-Benzoylaminoacrylic acids	M.P. °C	Yield %
1.	α-N-Benzoylamino-β-(p-methoxyphenyl)acrylic acid	235	68
2.	α-N-Benzoylamino-β-(3'-methoxy 4'-hydroxyphenyl) acrylic acid	210	65
3.	α-N-Benzoylamino-β-Cinnamylacrylic acid	214	64
4.	α-N-Benzoylamino-β-(o-methoxyphenyl)acrylic acid	218	56
5.	α-N-Benzoylamino-β-(p-hydroxyphenyl)acrylic acid	198	64
6.	α-N-Benzoylamino-β-(p-dimethylaminophenyl)acrylic acid	216	58
7.	α-N-Benzoylamino-β-(3',4'-dimethoxyphenyl)acrylic acid	174	73
8.	α-N-Benzoylamino-β-(2',4'-dihydroxyphenyl)acrylic acid	144	66
9.	α-N-Benzoylamino-β-furfurylacrylic acid	195	57
10.	α-N-Benzoylamino-β-(1'-napthyl)acrylic acid	192	58
11.	α-N-Benzoylamino-β-isopropylacrylic acid	118	66
12.	α-N-Benzoylamino-β-cyclohexylacrylic acid	162	52
13.	α-N-Benzoylamino-β-phenylacrylic acid	225	76
14.	α-N-Benzoylamino-β-(o-hydroxyphenyl)acrylic acid	202	72
15.	α-N-Benzoylamino-β-crotonylacrylic acid	168	62
16.	α-N-Benzoylamino-β-piperonylacrylic acid	158	61
17.	α-N-Benzoylamino-β-indolylacrylic acid	239	66

gently heating in dry benzene gives N-benzoylaminoacryloyl chloride (9)(Table 6).

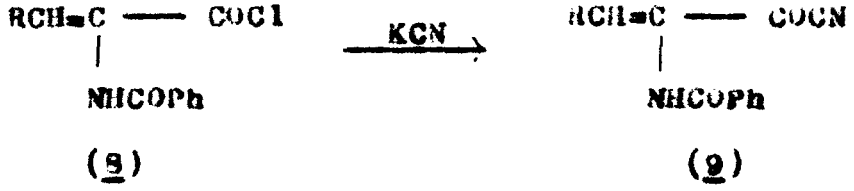
Table 6

Synthesis of N-Benzoylaminoacryloyl chlorides (9)

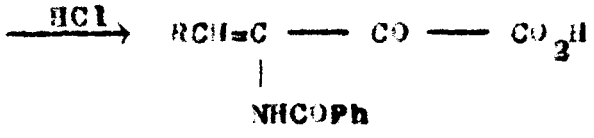
No.	N-Benzoylaminoacryloyl chlorides	M.P.°C	Yield %
1.	α-N-Benzoylamino-β(p-methoxyphenyl)acryloyl chloride	144	66
2.	α-N-Benzoylamino-β(3'-methoxy-4'-hydroxy)phenyl-acryloyl chloride	198	63
3.	α-N-Benzoylamino-β-Cinnamylacryloyl chloride	188	58
4.	α-N-Benzoylamino-β-(o-methoxyphenyl)acryloyl chloride	195	46
5.	α-N-Benzoylamino-β-(p-hydroxyphenyl)acryloyl chloride	136	56
6.	α-N-Benzoylamino-β-(p-dimethylaminophenyl)acryloyl chloride	166	48
7.	α-N-Benzoylamino-β-(3',4'-dimethoxyphenyl)acryloyl chloride	144	52
8.	α-N-Benzoylamino-β-(2',4'-dihydroxyphenyl)acryloyl chloride	132	54
9.	α-N-Benzoylamino-β-furfurylacryloyl chloride	153	65
10.	α-N-Benzoylamino-β-(1-napthyl)acryloyl chloride	170	56
11.	α-N-Benzoylamino-β-isopropylacryloyl chloride	108	62
12.	α-N-Benzoylamino-β-cyclohexylacryloyl chloride	156	48
13.	α-N-Benzoylamino-β-phenylacryloyl chloride	150	70
14.	α-N-Benzoylamino-β-(o-hydroxyphenyl)acryloyl chloride	174	68
15.	α-N-Benzoylamino-β-crotonylacryloyl chloride	159	58
16.	α-N-Benzoylamino-β-piperonylacryloyl chloride	132	42
17.	α-N-Benzoylamino-β-indolylacryloyl chloride	153	62

(c) Treatment of N-benzoylaminoacryloyl chloride with KCN Synthesis of 3-substituted Pyruvic acids

Acid chlorides can be converted to cyanides[333] with potassium cyanide which can be hydrolysed to corresponding acids[334]. N-benzoylaminoacryloyl chlorides were allowed to react with potassium cyanide solution under reflux for 19-25 hr when a clear solution was obtained, this was acidified using hydrochloric acid, it was again heated at reflux temperature yielding 3-substituted pyruvic acids 2 (Table 4).



(8) (9)



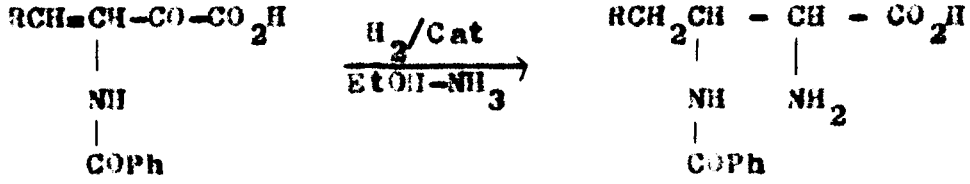
(2)

The IR, NMR spectra are identical with 2. Mentioned physical values including mixed melting points show identities when comparison are made between 3-substituted pyruvic acids obtained by two different routes.

III. Reductive Amination of 3-substituted Pyruvic acids synthesis of α-Amino-β-N-benzoylamino acids

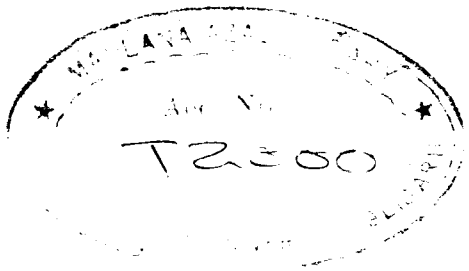
Published method show that azlactones as such do not undergo catalytic reduction at low pressure of hydrogen (45-65 psi) but acylaminoacrylic acids can be reduced smoothly.

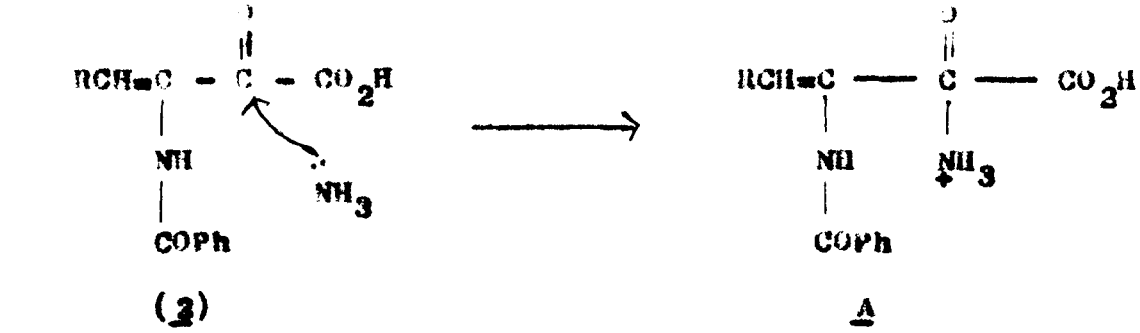
3-Substituted pyruvic acids can be successfully converted to dl-α-amino-β-N-benzoylamino acids 10 in high yield and with greater purity by catalytic reduction in presence of alcoholic ammonia and palladium charcoal (10% Pd) catalyst at elevated hydrogen pressure and room temperature when carbon-carbon double bond is reduced along with reductive amination of keto group.



(2) (10)

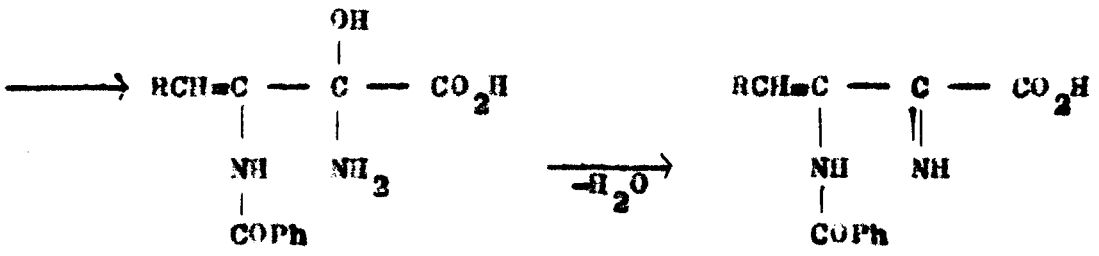
Ammonia reacts on the carbonyl group of keto acids resulting in a charge species A in which proton shift takes place giving dehydrated form B. The intermediate is then readily converted to α-amino-β-N-benzoylamino acid by the addition of hydrogen.



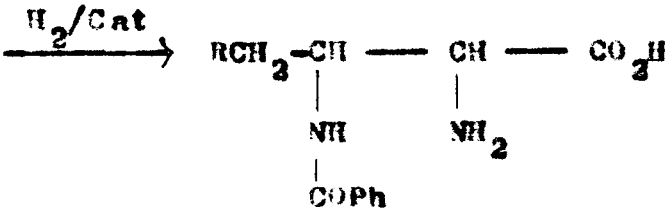


(2)

A



B



(10)

We have used Palladium charcoal (10% Pd) to catalyse reduction of 3-substituted pyruvic acid. In this case the compound is suspended in ethanol containing catalyst and sufficient quantity of ammonia solution (Sp. gr. 0.99). This is reduced in a Paar pressure catalytic hydrogenation apparatus under different hydrogen pressures (35-60 psi) for varying length of time (12-18 hr). When reduction is complete, the contents are filtered under hot condition. The combined filtrate and washings are evaporated to dryness under reduced

pressure and the residue crystallised from ethanol to give α-amino-β-N-benzoylamino acids (Table 7).

IR spectra shows characteristic NH stretching peak in the region 3010-3330 cm^{-1}. Bands in the region 1645-1725 cm^{-1} are assigned to amide CO stretching and bands at 1510-1580 cm^{-1} are due to NH deformation.

IV. Hydrolysis of α-Amino-β-N-Benzoylamino acids

Acid amides on treatment with acid or alkali are converted to carboxylic acids. Thus α-amino-β-N-benzoylamino acids are hydrolysed under reflux with an acid or alkali to the corresponding α,β-diamino acids. The hydrolysing agent used are hydrochloric acid barium hydroxide (Table 8).

On the basis of our experimental work we suggest that in the case of α-amino-β-N-benzoylamino acids 10, secondary amide linkage is hydrolysed to yield α,β-diamino acids 11. It involves nucleophilic substitution in which the amide group is replaced by hydroxyl group. Under acidic condition the amide is protonated to give 12 and water molecule is added resulting an intermediate 13 which gives α,β-diamino acid 11.

Table - 7

Synthesis of DL-α-Amino-β-N-Benzoylamino Acids (10)

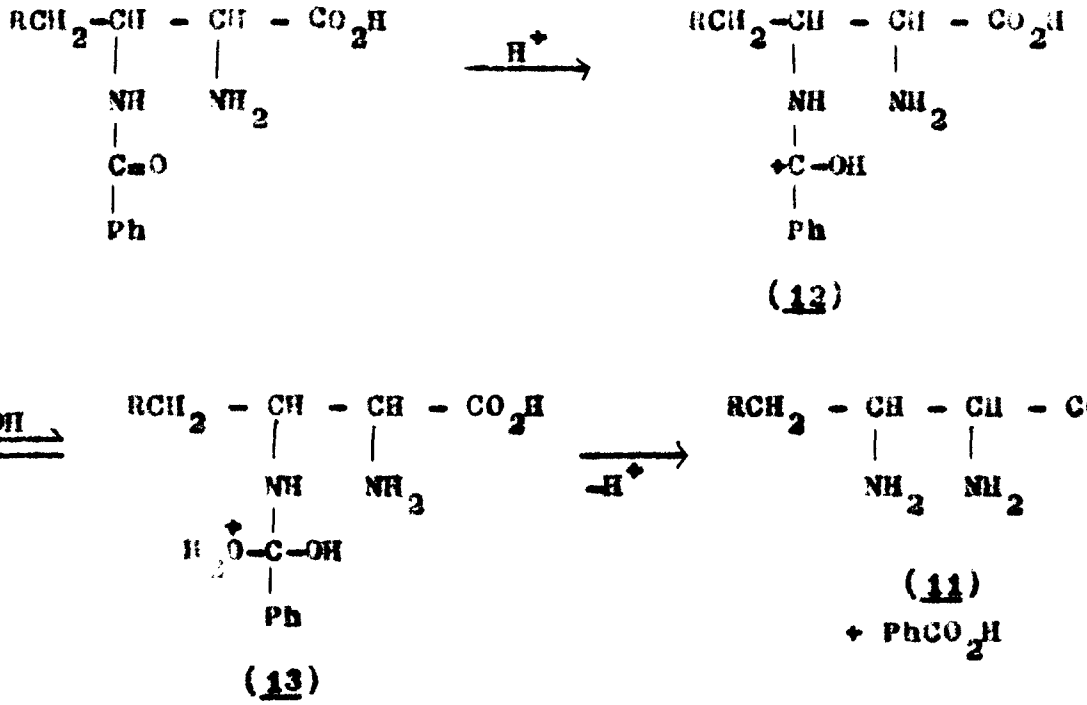
No.	Compounds	Hydrogen pressure psi	Reduction time hr	M.P. °C	Yield %
1.	DL-α-Amino-β-N-benzoylamino-(p-methoxyphenyl)butyric acid	39	16	142	81
2.	DL-α-Amino-β-N-benzoylamino-(3'-methoxy-4'-hydroxyphenyl)butyric acid	42	18	202	88
3.	DL-α-Amino-β-N-benzoylaminophenylhexanoic acid	46	14	165	88
4.	DL-α-Amino-β-N-benzoylamino-(o-methoxyphenyl)butyric acid	38	16	170	84
5.	DL-α-Amino-β-N-benzoylamino-(p-hydroxyphenyl)butyric acid	48	15	174	75
6.	DL-α-Amino-β-N-benzoylamino-(p-dimethylaminophenyl)butyric acid	55	14	115	70
7.	DL-α-Amino-β-N-benzoylamino-(3',4'-dimethoxyphenyl)butyric acid	54	16	138	90
8.	DL-α-Amino-β-N-benzoylamino-(2',4'-dihydroxyphenyl)butyric acid	52	15	146	78
9.	DL-α-Amino-β-N-benzoylaminofurfurylbutyric acid	48	18	158	86
10.	DL-α-Amino-β-N-benzoylamino-(1-napthyl)-butyric acid	46	16	178	82
11.	DL-α-Amino-β-N-benzoylaminoisopropyl butyric acid	50	15	142	76
12.	DL-α-Amino-β-N-benzoylaminocyclohexyl butyric acid	48	16	162	78
13.	DL-α-Amino-β-N-benzoylaminophenyl butyric acid	35	12	165	90
14.	DL-α-Amino-β-N-benzoylamino-(o-hydroxyphenyl)butyric acid	48	12	160	68
15.	DL-α-Amino-β-N-benzoylaminocrotonyl butyric acid	60	18	174	74
16.	DL-α-Amino-β-N-benzoylaminopiperonyl butyric acid	49	18	145	90
17.	DL-α-Amino-β-N-benzoylaminoindolyl butyric acid	44	18	162	90

Table - 8

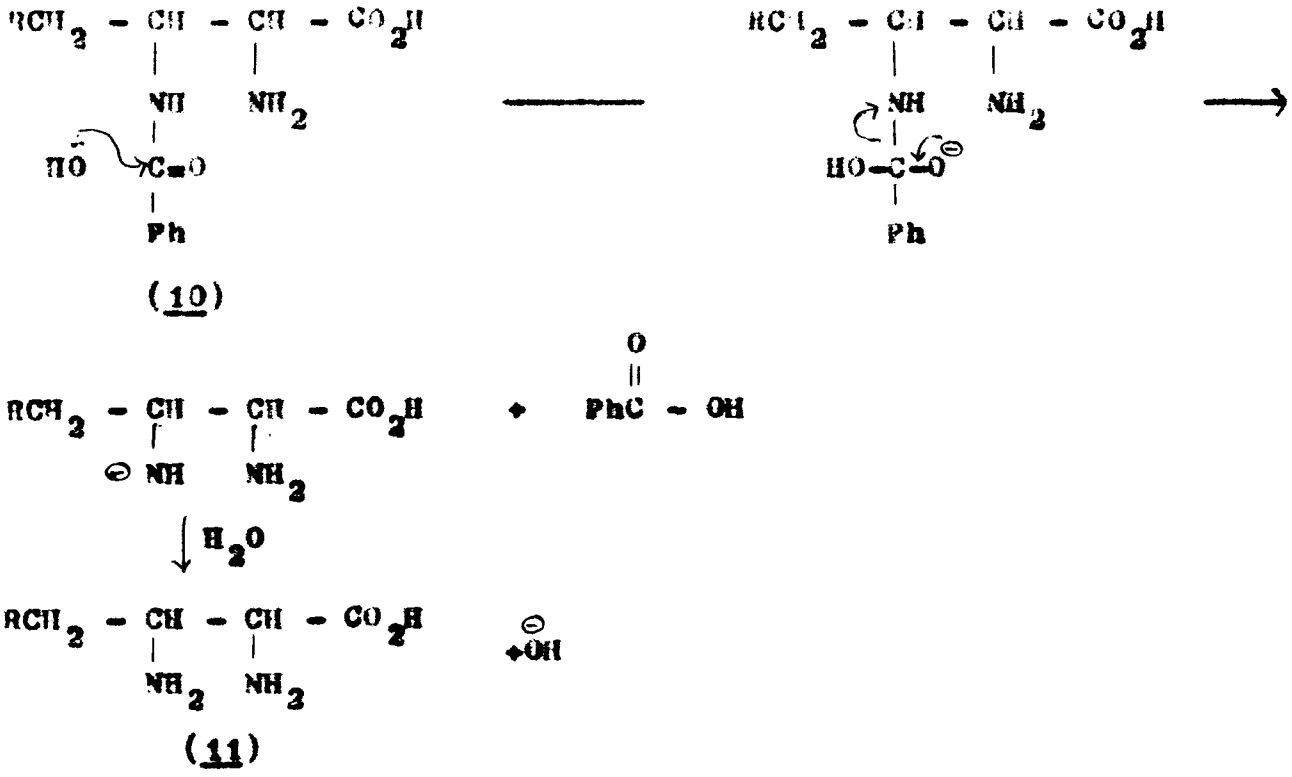
Synthesis of DL-α,β-Diamino Acids (11)

No.	Compounds	Hydrolysing agent	Reflux time hr	M.P. ^{o}C	Yield %
1.	DL-α,β-Diamino-γ-(p-methoxyphenyl) butyric acid	A	19	215	70
2.	DL-α,β-Diamino-γ-(3'-methoxy,4'-hydroxyphenyl)butyric acid	A	18	220	74
3.	DL-α,β-Diamino-ω-phenylhexanoic acid	A	19	215	70
4.	DL-α,β-Diamino-γ-(o-methoxyphenyl)butyric acid	A	21	225	75
5.	DL-α,β-Diamino-γ-(p-hydroxyphenyl)butyric acid	A	17	210	70
6.	DL-α,β-Diamino-γ-(p-dimethylaminophenyl)butyric acid	A	16	188	65
7.	DL-α,β-Diamino-γ-(3',4'-dimethoxyphenyl)butyric acid	A	19	218	67
8.	DL-α,β-Diamino-γ-(2',4'-dihydroxyphenyl)butyric acid	A	18	222	82
9.	DL-α,β-Diamino-γ-furfuryl butyric acid	B	24	202	75
10.	DL-α,β-Diamino-γ-(1-napthyl)butyric acid	B	22	226	78
11.	DL-α,β-Diamino-γ-isopropyl butyric acid	A	20	178	63
12.	DL-α,β-Diamino-γ-cyclohexyl butyric acid	A	16	218	74
13.	DL-α,β-Diamino-γ-phenyl butyric acid	A	18	235	85
14.	DL-α,β-Diamino-γ-(o-hydroxyphenyl)butyric acid	A	15	185	80
15.	DL-α,β-Diamino-γ-crotonyl butyric acid	A	16	210	70
16.	DL-α,β-Diamino-γ-piperonyl butyric acid	B	24	204	65
17.	DL-α,β-Diamino-γ-indolyl butyric acid	B	18	216	70

A = Hydrochloric acid (36 %) B = Barium hydroxide solution (15 %)



Under alkaline conditions hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the carbonyl group.



Subjection of α-amino-β-γ-benzoylamine acids to hydrolysis using hydrochloric acid for different period of time (15-24 hr) at reflux temperature lead to scission of benzoyl groups and permits the subsequent isolation of amino acids salt, on cooling and filtration of benzoic acid, separated. Amino acids salt thus obtained give amino acids on neutralisation with dilute ammonia in 60-90 percent yield .

In case of α,β-diamino-γ-piperonyl butyric acid, α,β-diamino-γ-indolyl butyric acid and α,β-diamino-γ-furfuryl butyric acid black pigments are formed when their benzoylamino acids 10 are hydrolysed using hydrochloric acid. However, hydrolysis of these benzoyl amino acids at reflux temperature using barium hydroxide solution (15%) gives α,β-diamino-γ-piperonyl butyric acid, α,β-diamino-γ-indolyl butyric acid and α,β-diamino-γ-furfuryl butyric acid in 65-75 percent yield. All amino acids are crystallised from ethanol (40-95%). Results obtained are shown in Table 8.

Characteristic IR spectra show broad band in the region 2765-3140 cm^{-1} for $\overset{+}{N}H_3$ and at 1560-1640 for COO group.

Experimental*

I. Preparation of Aglactone

1. Synthesis of 2-phenyl-4-(4'-methoxybenzal)-5-oxazolone

A mixture of a anisicaldehyde (13.6 g; 0.1 mol), powdered hippuric acid (17.9 g; 0.1 mol), powdered freshly fused sodium acetate, (8.2 g; 0.1 mol), and acetic anhydride (28.3 ml; 0.3 mol) was warmed on a boiling water bath for 30 minutes. Yellow crystals soon began to form and the whole liquid mass became solid. Water was added slowly to decompose acetic anhydride. The crystalline material thus secured was filtered, washed with ethanol (90%) and dried. This was recrystallised from ethyl acetate-ethanol mixture (3:1). Golden yellow needles thus obtained were filtered, dried when it weighed 22.3 g (80%) yield, m.p. 157-58° (Lit.[43] m.p. 158°).

2. Synthesis of 2-phenyl-4-(3'-methoxy 4'-acetoxybenzal)-5-oxazolone

An intimate mixture of vanillin (15.2 g; 0.1 mol), hippuric acid (17.9; 0.1 mol), and freshly fused powdered sodium acetate (16.4 g; 0.2 mol) was heated with acetic anhydride (28.3 ml; 0.3 ml) on a steam bath for 15 min. The reaction

*Melting points reported in this work were taken on a Kofler hot block are uncorrected in degree centigrade.

mixture was then grounded with water, filtered and washed several times with water. The crude product was crystallised from glacial acetic acid to give yellow needle m.p. 188-89° (lit.[43] m.p. 188-89°) and weighed 22.1 g (75%).

3. Synthesis of 2-phenyl-4-cinnamylidene-5-oxazolone

A mixture of cinnamaldehyde (26.4 g; 0.2 mol), hippuric acid (35.8 g; 0.2 mol), anhydrous sodium acetate (16.4 g; 0.2 mol) and acetic anhydride (56.5 ml; 0.5 mol) was heated on a steam bath under dry conditions. After few minutes of heating an intense yellow colour developed which changed to orange red and after 10 min., a clear solution was obtained. The flask was removed from the steam bath and kept at room temperature. On cooling a mass of orange coloured crystals was obtained. Water was added under cooled condition to decompose acetic anhydride and also to dissolve sodium acetate. This was then filtered, the crystalline mass was washed with water and then with five 10 ml portions of 95% ethanol to remove unreacted cinnamaldehyde. The azlactone thus obtained was crystallised from chloroform-ethanol mixture to give orange coloured needles melting at 151-52° (lit.[63] m.p. 152°) and weighed 33 g (60% yield).

4. Synthesis of 2-phenyl-4(2-methoxybenzal)-5-oxazolone

A mixture of o-methoxybenzaldehyde (13.6 g; 0.1 mol), hippuric acid (17.9g; 0.1 mol), powdered freshly fused sodium acetate (8.2 g; 0.1 mol) and acetic anhydride (28.3 ml; 0.3 mol) was heated on steam bath for 30 min. Yellow crystals soon began to separate and gradually the whole mass solidified. Ethanol was added to decompose acetic anhydride and the solid mass was filtered on a Buchner funnel, washed with hot water. Crystallisation from ethanol (85%) gave golden yellow needles m.p. 166-67° and weighed 20.01 g (75%)(lit.[335] m.p. 165-66°).

5. Synthesis of 2-phenyl-4-(4'-acetoxybenzal)-5-oxazolone

p-Hydroxybenzaldehyde (12.2 g; 0.1 mol), hippuric acid (17.9 g; 0.1 mol) and anhydrous sodium acetate (8.2 g; 0.1 mol) were finally powdered and mixed with acetic anhydride (28.3 ml; 0.2 mol). The mixture was kept on a boiling water bath for 10-15 minutes. On cooling the azlactone formed a solid cake. This was washed first with hot water and then with dilute ethanol. The crude azlactone (26.0 g) so obtained was dissolved in chloroform and precipitated by the addition of light petroleum ether (b.p. 40-60°). For further purification it was recrystallised from dilute alcohol to give yellow flate needles weighing 24.5 g(90% yield) m.p. 171-72° (lit.[338] m.p. 172-73°).

6. Synthesis of 2-phenyl-4-(4'-dimethylaminobenzal)-5-oxazolone

A mixture of hippuric acid (17.9 g; 0.1 mol) 4-dimethylaminobenzaldehyde (14.9 g; 0.1 mol), finally powdered fused sodium acetate (8.2 g; 0.1 mol) and acetic anhydride (40.8 ml; 0.4 mol) was refluxed for 20 min. The contents were poured into 100 ml of ice-cold water and filtered this was washed with plenty of water and once with ice-cold ethanol to remove unreacted aldehyde. Crystallisation from benzene yielded reddish brown needles, m.p. 232-33° (lit.[336] m.p. 210-11°), 13.5 g (69.2%).

7. Synthesis of 2-phenyl-4-(3',4'-dimethoxybenzal)-5-oxazolone

A mixture of (16.6 g; 0.1 mol) veratraldehyde (17.9 g; 0.1 mol) hippuric acid (8.2 g; 0.1 mol), fused sodium acetate and (28.3 ml; 0.3 mol) acetic anhydride was heated on an electric hot plate. As soon as the mixture liquified completely the flask was transferred to a steam bath and heated for 2 hr. At the end of this period 50 ml alcohol was added slowly to the content of the flask. During this addition the flask was cooled slightly to moderate the vigorousity of the reaction. After allowing the mixture to stand over night, the crystalline product was filtered and washed on the filter paper with two 20 ml portions of ice-cold alcohol and finally with two 20 ml portion of boiling water. The dried product weighed 21 g (71%) and melted at 147-48°. Recrystallisation from benzene improved the m.p. to 150-51° (lit.[15] m.p. 151-52°).

8. Synthesis of 2-phenyl-4-(2',4'-diacetoxybenzal)-5-oxazolone

A mixture of 2,4-dihydroxybenzaldehyde (or β-resorcylaldehyde)(13.8 g; 0.1 mol), hippuric acid (17.9; 0.1 mol) freshly fused sodium acetate (8.2 g; 0.1 mol) and acetic anhydride (28.3 ml; 0.3 mol) was heated on a free flame. As soon as the mixture liquified completely, the flask was transferred to a steam bath and heated for 2 hr. At the end of this period, 25 ml of ethanol was added slowly while cooling the flask. After allowing the mixture to stand overnight, the crystalline product was filtered on a Buchner funnel, washed with 20 ml portion of ice-cold ethanol and finally with two 20 ml portions of boiling water. On drying the product weighed 33.3 g (91.2%) and melted at 136-37° crystallisation from ethanol afforded buff coloured needles m.p. 139-40° (lit.[337] m.p. 130°).

9. Synthesis of 2-phenyl-4-(2'-furfurylidene)5-oxazolone

A mixture of hippuric acid (17.9 g; 0.1 mol), furfuraldehyde (9.7; 0.1 mol), anhydrous sodium acetate (8.2 g; 0.1 mol) and acetic anhydride (28.3 ml; 0.3 mol) was heated on a boiling water bath. After 10 min. the solution became clear, it was then cooled when it solidified to form an orange mass of crystals. Water was then added to decompose acetic anhydride and to dissolve sodium acetate and filtered the crystalline material was washed

with much water and then five times with 95% ethanol to remove traces of unreacted aldehyde. After crystallisation from benzene, the azlactone obtained as golden yellow needles, m.p. 170-71° (lit.[338] and weighed 11.5 g (48.3% yield).

10. Synthesis of 2-phenyl-4-(1'-napthylmethylene)5-oxazolone

A mixture of 1-napthaldehyde (15.6 g; 0.1 mol), hippuric acid, (17.9 g; 0.1 mol), freshly fused sodium acetate (8.2 g; 0.1 mol) and acetic anhydride (30 ml; 0.3 mol) was fused on a free flame in a conical flask and then heated on a steam bath for 1 hr. After cooling, 30 ml of ethanol (95%) was added to the reaction mixture and then left overnight at room temperature. The crude product was filtered on Buchner funnel, washed with three 50 ml portions of hot water and once with cold ethanol. It was recrystallised from ethanol (95%), yellow needle shaped crystals, thus obtained were filtered and dried yield 18.8 g (62.9%) m.p. 174-75° (lit.[339] m.p. 170-71°).

11. Synthesis of 2-phenyl-4-isopropylidene-5-oxazolone

A mixture of hippuric acid (17.9 g; 0.1 mol), acetone (58 g; 2.0 mol), acetic anhydride (30 ml; 0.3 mol) and freshly fused sodium acetate (8.2 g; 0.1 mol) was heated under reflux at 110° for 6 hr. In the early stages of the reaction a pasty

solid separated which slowly dissolved yielding a pink solution. The solid which separated when the cooled solution was poured into a large volume of water was collected, washed with aqueous sodium bicarbonate to remove benzoic acid and recrystallised from alcohol. The oxazolone was obtained in needles, m.p. 99-100° (lit.[340] m.p. 99-100°) and weighed 10.5 g (39% yield).

12. Synthesis of 2-phenyl-4-cyclohexylidene-5-oxazolone

A mixture of hippuric acid (53.8 g; 0.3 mol), freshly fused sodium acetate (24.6 g; 0.3 mol), acetic anhydride (65.8 ml; 0.7 mol) and cyclohexanone (30 g; 0.3 mol) was heated on a steam bath for 45 min. to yield a light red solution. The reaction mixture was then reduced to a volume of 25 ml under reduced pressure when a portion of the oxazolone precipitated out. It was filtered and the mother liquor cooled for few hours, suspended in ethanol and poured into 2 litre of ice-cold water with continuous stirring. The aqueous phase was decanted and the precipitated material was dissolved in hot ethanol. On chilling, the oxazolone emerged out as red needles. This was filtered and dried when it weighed 17.4 g (34.6%), m.p. 140°. Recrystallisation from ethanol (95%) yielded 17.0 g of the product m.p. 142° (lit. [341] m.p. 142°).

13. Synthesis of 2-phenyl-4-benzal-5-oxazolone

A mixture of (10.6 g; 0.1 mol) benzaldehyde (17.9 g; 0.1 mol), hippuric acid (9.2 g; 0.1 mol), fused sodium acetate and acetic anhydride (28.3 ml; 0.3 ml) was heated on an electric hot plate till it melted completely. The flask was then transferred to a steam bath for two hours. At the end of this period 40 ml of ethanol (95%) was added slowly while cooling it under cold water through shaking. The mixture was then allowed to ~~stand overnight~~ crystalline product thus separated was filtered on Buchner funnel under suction, washed with two 20 ml portions of ice-cold ethanol and finally with two 20 ml portions of boiling water. The product on drying weighed 15.6 g (62%), m.p. 165-66°. This was recrystallised from benzene, m.p. 167-68° (lit.[342] m.p. 167-68°).

14. Synthesis of 2-phenyl-4(2'-acetoxybenzal)-5-oxazolone

A mixture of salicylaldehyde (12.2 g; 0.1 mol), hippuric acid (17.9; 0.1 mol), anhydrous potassium carbonate (13.8 g; 0.1 mol), and acetic anhydride (28.3 ml; 0.3 mol) was stirred at room temperature. The temperature of the reaction was then raised to about 100° when it set into a yellow crystalline mass which was left overnight at room temperature and then triturated with hot water, granular material thus obtained was filtered, washed with ethanol and dried. Crystallisation from ethanol (95%) gave golden yellow crystals m.p. 138-39° and weighed 21.8 g (71%)(lit.[7] m.p. 137-38°).

15. Synthesis of 2-phenyl-3-crotonylidene-5-oxazolone

To a mixture of hippuric acid (17.9 g; 0.1 mol), anhydrous potassium carbonate (13.9 g; 0.1 mol) and acetic anhydride (28.3 ml; 0.3 mol)(7.7 g; 0.11 mol) of crotonaldehyde was added dropwise with constant stirring. The solution turned gradually red while the temperature rose to 100°C. The stirring was continued till the reaction mixture solidified and then left overnight. Acetic anhydride was decomposed with water and the precipitated oxazolone filtered, washed with water and then with ice-cold ethanol crystallisation from ethanol, yielded pink needles shaped crystals, m.p. 163-64°, yield 9.5 (40%).

16. Synthesis of 2-phenyl-4-piperonalmethylene-5-oxazolone

Piperonal (15 g; 0.1 mol), hippuric acid (17.9 g; 0.1 mol) acetic anhydride (34.4 ml; 0.2 mol) and potassium bicarbonate (10 g; 0.1 mol) were stirred together at room temperature, and then allowed to stand overnight at room temperature. The oxazolone obtained on addition of hot water (150 ml) was filtered and washed with dilute acetic acid followed by water. The dried material weighed 20 g (82%). On recrystallisation from ethanol (95%), it melted at 197-98° (lit.[37] m.p. 195-97°).

17. Synthesis of 2-phenyl-4-(3'-indolylmethylene)-5-oxazolone

Hippuric acid (18 g, 0.1 mol) and potassium bicarbonate (4.0 g; 0.04 mol) were dissolved in acetic anhydride (40 ml; 0.4 mol) with stirring, indolyl-3-aldehyde (14.5 g; 0.1 mol) was then added. The mixture was stirred for 1 hr. Crystalline product thus obtained was then poured into 200 ml of hot water. The precipitated oxazolone was filtered after 3 hr, washed with water and dried. Yield 23.1 g (90%) m.p. 184-85°.

A. FORMIC ACID PROCESS

II. Synthesis of 3-Substituted Pyruvic acids

1. Synthesis of 3-N-Benzoylamino-3-(p-methoxybenzal)pyruvic acid

2-Phenyl-4-(4'-methoxybenzal)-5-oxazolone (3 g) was dissolved in 25 ml of anhydrous formic acid. This was heated under reflux for 30 min. Formic acid was removed under reduced pressure when crystalline mass of 3-N-Benzoylamino-3-(p-methoxybenzal)pyruvic acid emerged out. This was filtered and the crystalline product thus obtained was recrystallised from ethanol yielding 4.08 g (72%), m.p. 206°; UV λ_{max}^{MeOH} 230 and 3.05 nm; IR (Nujol) 3225, 1740, 1690, 1650, 1600, 1510, 1460, 1375, 1330, 1250 cm^{-1}; NMR (CCl_4) 9.6, 8.6, 8.2, 6.4, 2.4 δ.

Anal. for $C_{18}H_{15}O_5N$

Calcd: C, 66.45; H, 4.65; N, 4.31.

Found: C, 66.43; H, 4.60; N, 4.29.

2. Synthesis of 3-N-Benzoylamino-3-(3'-methoxy-4'-hydroxybenzal)pyruvic acid

Powdered 2-phenyl-4-(3'-methoxy-4'-acetoxybenzal)-5-oxazolone (5 g) was gently heated under reflux with anhydrous formic acid (25 ml) for 30 min. Excess of formic acid was removed under diminished pressure. This was cooled when white crystalline acid was separated on Buchner funnel and was

recrystallised from ethanol. The dried product weighed 3.93 g (70 %), m.p. 178°; UV λ_{max}^{MeOH} 220 nm; IR (Nujol) 3290, 2650, 1750, 1720, 1680; NMR (CCl_4) 9.3, 8.4, 7.8, 6.8, 6.4, 2.4 δ.

Anal. for $C_{19}H_{15}O_6N$

Calcd: C, 63.34; H, 4.43; N, 4.10.

Found: C, 63.33; H, 4.44; N, 4.0.

3. Synthesis of 3-N-Benzoylamino-3-cinnamylidene pyruvic acid

Powdered 2-phenyl-4-cinnamylidene-5-oxazolone (5 g) was taken in 25 ml of anhydrous formic acid. This was heated at reflux temperature for 30 min. The solvent was evaporated under diminished pressure and the residue so secured was dissolved in ethanol, on cooling the product crystallised out. This was filtered and dried, yield 3.37 g (65 %), m.p. 225°; UV λ_{max}^{MeOH} 225 nm; IR (Nujol) 3255, 1760, 1710, 1640, 1620, 1585, 1540, 1372, 1280 cm^{-1}; NMR (CCl_4) 9.4, 8.6, 7.4, 6.6 δ.

Anal. for $C_{19}H_{15}O_4N$

Calcd: C, 71.02; H, 4.71; N, 4.36.

Found: C, 71.01; H, 4.68; N, 4.32.

4. Synthesis of 3-N-Benzoylamino-3-(o-methoxybensal)pyruvic acid

2-Phenyl-4-(2-methoxybenzal)-5-oxazolone (5 g) was dissolved in anhydrous formic acid (25 ml). This was heated

at reflux temperature for 30 min. Excess of solvent was evaporated under reduced pressure. The residue was crystallised from ethanol (95%). This was filtered. Yield 4.31 g (85%), m.p. 201°; UV λ_{max}^{MeOH} 230, 280 nm; IR (Nujol) 3260, 1750, 1730, 1650, 1610, 1490, 1310, 1240 cm^{-1}; NMR (CCl_4) 9.3, 8.4, 7.8, 6.6, 2.4 δ.

Anal. for $C_{18}H_{15}O_5N$

Calcd: C, 66.45; H, 4.65; N, 4.31.

Found: C, 66.39; H, 4.51; N, 4.29.

5. Synthesis of 3-N-Benzoylamino-3-(p-hydroxybenzal)pyruvic acid

In anhydrous formic acid (25 ml), 2-phenyl-4-(4'-acetoxy-benzal)-5-oxazolone (5 g) was added, which was heated at reflux temperature for 30 min. The solvent was then removed under diminished pressure. The crystalline product obtained using ethanol as solvent was filtered when it weighed 3.75 g (60%) and melted at 320°; UV λ_{max}^{MeOH} 220, 240 nm; IR (Nujol) 3200, 2715, 1760, 1665, 1603, 1570, 1510, 1460, 1390, 1275 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 7.8, 6.6, 6.2 δ.

Anal. for $C_{17}H_{13}O_5N$

Calcd: C, 65.59; H, 4.21; N, 4.50.

Found: C, 65.60; H, 4.19; N, 4.49.

6. Synthesis of 3-N-Benzoylamino-3-(p-dimethylaminobenzal) pyruvic acid

Powdered 2-phenyl-4-(4'-dimethylaminobenzal)-5-oxazolone (5 g) was heated at reflux temperature with anhydrous formic acid (35 ml) for 3 min. The solvent was removed under reduced pressure. The residue was crystallised through ethanol (95%). This was filtered and weighed 3.58 g(58%) m.p. 158°; UV λ_{max}^{MeOH} 230, 360 nm; IR (Nujol) 3290, 2710, 1775, 1720, 1680, 1640, 1570, 1530, 1490, 1360, 1240 cm^{-1}; NMR (CCl_4) 9.2, 8.6, 8.4, 7.8, 6.6 δ.

Anal. for $C_{19}H_{17}O_4N_3$

Calcd: C, 67.60; H, 5.0; N, 8.31.

Found: C, 67.58; H, 5.0; N, 8.30.

7. Synthesis of 3-N-Benzoylamino-3-(3',4'-dimethoxybenzal) pyruvic acid

3-Phenyl-4-(3',4'-dimethoxybenzal)-5-oxazolone (5 g) was suspended in anhydrous formic acid (25 ml). This was gently heated to reflux temperature for 30 min. Excess of solvent was removed under diminished pressure and the residue so secured was crystallised with ethanol (95%). This was filtered and dried. Yield 4.82 g (95%), m.p. 190°; UV λ_{max}^{MeOH} 230, 255 nm; IR (Nujol) 3290, 2750, 1775, 1710, 1680, 1640, 1610, 1500, 1460, 1370, 1280 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 7.8, 6.6, 2.4 δ.

Anal. for $C_{19}H_{17}O_6N$

Calcd: C, 64.22; H, 4.82; N, 3.94.

Found: C, 64.21; H, 4.80; N, 3.88.

8. Synthesis of 3-N-Benzoylamino-3-(2',4'-dihydroxybenzal) pyruvic acid

2-Phenyl-4-(2',4'-diacetoxybenzal)-5-oxazolone (5 g) was heated under reflux with anhydrous formic acid (25 ml) for 30 min. The solvent was reduced under diminished pressure. This was crystallised using ethanol (95%), filtered and dried when it melted at 160° and weighed 3.95 g (69%); UV λ_{max}^{MeOH} 220, 240 nm; IR (Nujol) 3300, 2710, 2115, 1730, 1740, 1660, 1620, 1540, 1490, 1370, 1260 cm^{-1}; NMR (CCl_4) 9.2, 8.6, 7.4, 6.4, 6.2 δ.

Anal. for $C_{17}H_{13}O_6N$

Calcd: C, 62.38; H, 4.0; N, 4.28.

Found: C, 62.36; H, 4.0; N, 4.26.

9. Synthesis of 3-N-Benzoylamino-3-furfurylidene pyruvic acid

2-Phenyl-4-(2'-furfurylidene)-5-oxazolone (5 g) was dissolved in 25 ml of anhydrous formic acid. This was heated under reflux for 30 min. Excess of solvent was removed under reduced pressure when a crystalline mass was obtained. This was recrystallised from ethanol and filtered, when it weighed 4.54 g (84%) and melted at 210°; UV λ_{max}^{MeOH} 240, 280 nm; IR (Nujol) 3380, 2360, 1940, 1780, 1670, 1640, 1580, 1550, 1510, 1450, 1370, 1270 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 8.4, 7.8, 6.6, 6.3 δ.

Anal. for $C_{15}H_{11}O_5N$

Calcd: C, 63.16; H, 3.89; N, 4.91.

Found: C, 63.00; H, 3.86; N, 4.88.

10. Synthesis of 3-N-Benzoylamino-3-(1'-napthylidene) pyruvic acid

2-Phenyl-4-(1'-napthylmethylene)-5-oxazolone (5 g) was gently heated under reflux with 25 ml of formic acid (98-100%) for 30 min. The solvent was removed under diminished pressure. Ethanol (95%) was added when a white crystalline product emerged out. This was filtered and dried. Yield 3.75 g (64%), m.p. 218°; UV λ_{max}^{MeOH} 230, 280 nm; IR (Nujol) 3270, 2180, 1795, 1740, 1680, 1540, 1470, 1360, 1340, 1275, 1240 cm^{-1}; NMR (CCl_4) 9.4, 8.6, 7.9, 6.6, 6.2 δ.

Anal. for $C_{21}H_{15}O_4N$

Calcd: C, 73.03; H, 4.38; N, 4.06.

Found: C, 73.00; H, 4.36; N, 4.01.

11. Synthesis of 3-N-Benzoylamino-3-isopropylidene pyruvic acid

Powdered 2-phenyl-4-isopropylidene-5-oxazolone (5 g) was taken in 25 ml of anhydrous formic acid. This was heated at reflux temperature for 30 min. The solvent was evaporated under reduced pressure and the residue so secured was dissolved in ethanol (95%). On cooling the while product crystallised out. This was filtered and dried. Yield 4.08 g (82%), m.p. 128°; UV λ_{max}^{MeOH} 230 nm; IR (Nujol) 3270, 2140, 1760, 1700, 1680, 1640, 1590, 1510, 1420, 1360, 1240 cm^{-1}; NMR (CCl_4) 9.0, 8.4, 8.2, 7.8, 6.6 δ.

Anal. for $C_{13}H_{13}O_4N$

Calcd: C, 63.15; H, 5.30; N, 5.67.

Found: C, 63.14; H, 5.29; N, 5.66.

12. Synthesis of 3-N-Benzoylamino-3-cyclohexylidene pyruvic acid

2-Phenyl-4-cyclohexylidene-5-oxazolone (5 g) was dissolved in anhydrous formic acid (25 ml). This was refluxed for 30 min. Excess of solvent was evaporated under diminished pressure. The residue was crystallised using ethanol (95%). This was filtered, dried and weighed 3.73 g (56%), m.p. 188°; UV λ_{max}^{MeOH} 240 mμ; IR (Nujol) 3290, 2110, 1770, 1740, 1670, 1620, 1540, 1480, 1390, 1330, 1290, 1240 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 8.4, 7.8, 6.8, 6.4 δ.

Anal. for $C_{16}H_{17}O_4N$

Calcd: C, 66.88; H, 5.96; N, 4.88.

Found: C, 66.84; H, 5.90; N, 4.86.

13. Synthesis of 3-N-Benzoylamino-3-benzalpyruvic acid

In anhydrous formic acid (25 ml), 2-phenyl-4-benzal-5-oxazolone (5 g) was added. This was heated at reflux temperature for 30 min. The solvent was then reduced under diminished pressure. The crystalline mass thus obtained was crystallised using ethanol (95%) and filtered, when 5.85g(95%)acid was obtained and melted at 252°; UV λ_{max}^{MeOH} 230, 290 mμ; IR (Nujol) 3300, 2650, 1795, 1680,1635, 1598, 1572, 1460 cm^{-1}; NMR (CCl_4) 9.7, 9.4, 8.2, 6.9 δ.

Anal. for $C_{17}H_{13}O_4N$

Calcd: C, 69.14; H, 4.40; N, 4.74.

Found: C, 69.01; H, 4.41; N, 4.76.

14. Synthesis of 3-N-Benzoylamino-3-(o-hydroxybenzal) pyruvic acid

Powdered 3-phenyl-4-(2'-acetoxybenzal)-5-oxazolone (5 g) was heated at reflux temperature in anhydrous formic acid (25 ml) for 30 min. The solvent was removed under reduced pressure. The residue was crystallised through ethanol (95%). This was filtered, dried and weighed 3.75 g (60%), m.p. 115°; UV λ_{max}^{MeOH} 230, 260 nm; IR (Nujol) 3300, 2720, 1760, 1700, 1660, 1590, 1520, 1440, 1360, 1340, 1290 cm^{-1}; NMR (CCl_4) 9.4, 8.6, 7.4, 6.6 δ.

Anal. for $C_{17}H_{13}O_5N$

Calcd: C, 65.59; H, 4.21; N, 4.50

Found: C, 65.61; H, 4.20; N, 4.48.

15. Synthesis of 3-N-Benzoylamino-3-crotonylidenepyruvic acid

2-Phenyl-3-crotonylidene-5-oxazolone (5 g) was suspended in anhydrous formic acid (25 ml). This was heated at reflux temperature for 30 min. Solvent was removed under diminished pressure and the residue so obtained was crystallised using ethanol (95%) this was filtered and dried. Yield 4.17 g (68%), m.p. 192°; UV λ_{max}^{MeOH} 220, 240 nm; IR (Nujol) 3280, 2170, 1760, 1730, 1640, 1610, 1570, 1480, 1420, 1370, 1280, 1260 cm^{-1}; NMR (CCl_4) 9.3, 8.6, 8.4, 7.4, 6.6 δ.

Anal. for $C_{14}H_{13}O_4N$

Calcd: C, 64.96; H, 5.05; N, 5.40.

Found: C, 64.88; H, 5.00; N, 5.38.

16. Synthesis of 3-Benzoylamino-3-piperonylidenepyruvic acid

2-Phenyl-4-piperonal-methylene-5-oxazolone (5 g) was heated at reflux temperature with anhydrous formic acid (25 ml) for 30 min. The solvent was removed under diminished pressure. The residue was crystallised using ethanol (95%). This was filtered and dried when it melted at 179° and weighed 4.80 (94%); UV λ_{max}^{MeOH} 230, 265 nm; IR (Nujol) 3290, 2740, 1770, 1710, 1680, 1640, 1510, 1460, 1370, 1250 cm^{-1}; NMR (CCl_4) 9.4, 8.4, 7.8, 6.8, 6.3, 4.4 δ.

Anal. for $C_{18}H_{13}O_5N$

Calcd: C, 66.87; H, 4.05; N, 4.33.

Found: C, 66.86; H, 4.00; N, 4.30.

17. Synthesis of 3-N-Benzoylamino-3-indolylidene pyruvic acid

2-Phenyl-4-(3'-indolylmethylene)-5-oxazolone was suspended in anhydrous formic acid (25 ml). This was heated at reflux temperature till a clear solution was obtained. The solvent was removed under reduced pressure. Ethanol was added to the residue when crystalline mass emerged out. This was filtered, dried and weighed 4.59 g (89%), m.p. 240°; UV λ_{max}^{MeOH} 230, 280 nm; IR (Nujol) 3290, 1780, 1740, 1680, 1620, 1570, 1540, 1480, 1360, 1240 cm^{-1}; NMR (Nujol) 9.2, 8.6, 8.2, 7.4, 6.2 δ.

Anal. for $C_{19}H_{14}O_4N_2$

Calcd: C, 68.25; H, 4.22; N, 8.38.

Found: C, 68.21; H, 4.20; N, 8.40.

II. B. CYANIDE PROCESS

(a) Synthesis of N-Benzoylaminoacrylic acids

1. Synthesis of α-N-Benzoylamino-β-(p-methoxyphenyl) acrylic acid

2-Phenyl-4-(4'-methoxybenzal)-5-oxazolone (5 g) was heated under reflux for 20 min. with sodium hydroxide solution (15%; 20 ml). After cooling, the solution was acidified to congo red, with dilute hydrochloric acid to the appearence of the acid which was filtered, washed with cold water and dried, m.p. 235°, yield 4.0 g (68%).

Anal. for $C_{17}H_{15}O_4N$

Calcd: C, 68.67; H, 5.08; N, 4.71.

Found: C, 68.66; H, 5.08; N, 4.70.

2. Synthesis of α-N-Benzoylamino-β-(3'-methoxy-4'-hydroxyphenyl)acrylic acid

Powdered 2-phenyl-4-(3'-methoxy-4'-acetoxybenzal)-5-oxazolone (5 g) was refluxed with gentle heating for 20 min. with sodium hydroxide (15%; 20 ml). The solution was acidified when cold. In the red colour solution the crystals of the product emerged out, these were recrystallised from ethanol. The crystalline mass was filtered, dried and weighed 3.90 g (65%), m.p. 210°.

Anal. for $C_{17}H_{15}O_5N$

Calcd: C, 65.17; H, 4.79; N, 4.47.

Found: C, 65.16; H, 4.80; N, 4.46.

3. Synthesis of α-N-Benzoylamino-β-cinnamylacrylic acid

2-Phenyl-4-cinnamylidene-5-oxazolone (5 g) was taken in sodium hydroxide solution (20 ml; 15%). This was heated at reflux temperature for 20 min. The solution was acidified with hydrochloric acid, when it turned red, crystals of the product thus obtained, when cooled, were recrystallised from methanol. Yield 3.94 g (64%), m.p. 214°.

Anal. for $C_{19}H_{15}O_3N$

Calcd: C, 73.70; H, 5.15; N, 4.78.

Found: C, 73.68; H, 5.14; N, 4.77.

4. Synthesis of α-N-Benzoylamino-β-(o-methoxyphenyl) acrylic acid

2-Phenyl-4-(2-methoxybenzal)-5-oxazolone (5 g) was dissolved in sodium hydroxide solution (15%; 20 ml). This was heated at reflux temperature for 30 min and then acidified with hydrochloric acid, when it turned red. On cooling the crystalline mass was obtained. This was recrystallised from methanol which was filtered and weighed 3.69 g (56%), m.p. 218°.

Anal. for $C_{17}H_{15}O_4N$

Calcd: C, 68.67; H, 5.08; N, 4.71.

Found: C, 68.66; H, 5.08; N, 4.70.

5. Synthesis of α-N-Benzoyl-β-(p-hydroxyphenyl)acrylic acid

Powdered 2-phenyl-4-(4'-acetoxybenzal)-5-oxazolone (5 g) was heated with sodium hydroxide solution (20 ml; 50%) at reflux temperature for 20 min. The solvent was then acidified with hydrochloric acid. The residue obtained on colling was crystallised using methanol. This was filtered, when it weighed 3.99 g (64 %), m.p. 198°.

Anal. for $C_{16}H_{13}O_4N$

Calcd: C, 67.94; H, 6.63; N, 4.95.

Found: C, 67.93; H, 6.64; N, 4.94.

6. Synthesis of α-N-Benzoyl-β-(p-dimethylaminophenyl) acrylic acid

2-Phenyl-4-(4'-dimethylaminobenzal)-5-oxazolone (5 g) was heated at reflux temperature with sodium hydroxide solution (15%; 20 ml) for 20 min. The solution was acidified with hydrochloric acid. The residue thus obtained was crystallised on cooling, through methanol. This was filtered and weighed 3.69 g (59 %), m.p. 216°.

Anal. for $C_{18}H_{18}O_3N$

Calcd: C, 69.67; H, 5.80; N, 9.0.

Found: C, 69.66; H, 5.78; N, 9.0.

7. Synthesis of α-N-Benzoylamino-β-(3',4'-dimethoxyphenyl) acrylic acid

2-Phenyl-4-(3',4'-dimethoxybenzal)-5-oxazolone (5 g) was suspended in sodium hydroxide solution (20 ml; 15%). This was gently heated to reflux temperature for 20 min. The solution was then acidified with hydrochloric acid, when it became red, on cooling the product obtained was crystallised using methanol. The crystalline mass thus obtained was filtered and dried. Yield 4.11 g (73%), m.p. 174°.

Anal. for $C_{18}H_{17}O_5N$

Calcd: C, 66.05; H, 5.14; N, 4.28.

Found: C, 66.05; H, 5.13; N, 4.26.

9. Synthesis of α-N-Benzoylamino-β-(3',4'-dihydroxyphenyl) acrylic acid

2-Phenyl-4-(3',4'-diacetoxybenzal)-5-oxazolone (5 g) was heated at reflux temperature with sodium hydroxide solution (20 ml; 15%) for 20 min. This was then acidified with hydrochloric acid till the solution became red, on cooling the residue obtained was crystallised from methanol, this was filtered and dried when it melted at 144° and weighed 3.98 g (66%).

Anal. for $C_{16}H_{13}O_5N$

Calcd: C, 64.21; H, 4.34; N, 4.68.

Found: C, 64.20; H, 4.35; N, 4.67.

9. Synthesis of α-N-Benzoylamino-β-furfurylacrylic acid

2-Phenyl-4-(2'-furfurylidene)-5-oxazolone (5 g) was dissolved in sodium hydroxide solution (20 ml; 15%). This was heated under reflux for 20 min. The solution was acidified with hydrochloric acid till it turned red, on cooling the product obtained was filtered and crystallised using methanol, this was filtered and dried when it weighed 3.83 g (57%) and melted at 195°.

Anal. for $C_{14}H_{11}O_4N$

Calcd: C, 65.36; H, 4.31; N, 5.45.

Found: C, 65.35; H, 4.30; N, 5.44.

10. Synthesis of α-N-Benzoylamino-β-(1'-napthyl)acrylic acid

2-Phenyl-4-(1'-napthylmethylene)-5-oxazolone (5 g) was gently heated under reflux with sodium hydroxide solution (20 ml; 15%) for 20 min. The solution was then acidified with hydrochloric acid when a red coloured solution was obtained. On cooling crystalline product emerged out, this was recrystallised from methanol, filtered, dried when it weighed 3.63 g (58%), m.p. 192°.

Anal. for $C_{20}H_{15}O_3N$

Calcd: C, 75.69; H, 4.76; N, 4.41.

Found: C, 75.66; H, 4.75; N, 4.40.

11. Synthesis of α-N-Benzoylamino-β-isopropylacrylic acid

Powdered 2-phenyl-4-isopropylidene-5-oxazolone (5 g) was taken in sodium hydroxide solution (20 ml; 15%). This was heated at reflux temperature for 20 min. The solution was then acidified with hydrochloric acid, when crystalline product was obtained using methanol. This was filtered and dried. Yield 4.21 g (66%), m.p. 118°.

Anal. for $C_{12}H_{13}O_3N$

Calcd: C, 65.75; H, 5.98; N, 6.39.

Found: C, 65.74; H, 5.83; N, 6.40.

12. Synthesis of α-N-Benzoylamino-β-cyclohexylacrylic acid

2-Phenyl-4-cyclohexylidene-5-oxazolone (5 g) was dissolved in sodium hydroxide solution (15%; 20 ml). This was heated at reflux temperature for 30 min. The solution was acidified with hydrochloric acid till it turned red, the product thus obtained on cooling was crystallised from methanol. This was filtered and dried when it weighed 3.65 g (53%), m.p. 162°.

Anal. for $C_{16}H_{17}O_3N$

Calcd: C, 70.83; H, 6.32; N, 5.16.

Found: C, 70.80; H, 6.30; N, 5.15.

13. Synthesis of α-N-Benzoylamino-β-phenylacrylic acid

2-Phenyl-4-benzal-5-oxazolone (5 g) was added to sodium hydroxide solution (30 ml; 15%), this was heated at reflux temperature for 20 min. The solution was then acidified with hydrochloric acid, when it turned red, on cooling a residue was obtained, this was crystallised using methanol. The crystalline material thus obtained was filtered, dried when it weighed 4.35 g (76%), m.p. 225°.

Anal. for $C_{16}H_{13}O_3N$

Calcd: C, 71.90; H, 4.90; N, 5.24.

Found: C, 71.89; H, 4.96; N, 5.22.

14. Synthesis of α-N-Benzoylamino-β-(o-hydroxyphenyl) acrylic acid

Powdered 2-phenyl-4-(2'-acetoxybenzal)-5-oxazolone (5 g) was heated at reflux temperature with sodium hydroxide solution (30 ml; 15%) for 30 min. The solution was acidified with hydrochloric acid and cooled when a red product was obtained, this was crystallised using methanol and filtered when it weighed 4.20 g (72%) and melted at 202°.

Anal. for $C_{16}H_{13}O_4N$

Calcd: C, 67.84; H, 6.63; N, 4.95.

Found: C, 67.90; H, 6.60; N, 4.88.

15. Synthesis of α-N-Benzoylamino-β-crotonylacrylic acid

2-Phenyl-3-crotonylidene-5-oxazolone (5 g) was suspended in sodium hydroxide solution (20 ml, 15%) for 20 min. This was then acidified with hydrochloric acid, when on cooling a crystalline mass obtained. This was recrystallised using methanol, filtered, dried, when it weighed 4.04 g (62), m.p. 188°.

Anal. for $C_{15}H_{13}O_3N$

Calcd: C, 70.58; H, 5.13; N, 5.49.

Found: C, 70.49; H, 5.10; N, 5.44.

16. Synthesis of α-N-Benzoylamino-β-piperonylacrylic acid

2-Phenyl-4-piperonalmethylene-5-oxazolone (5 g) was heated at reflux temperature with sodium hydroxide solution (20 ml, 15%) for 20 min. The resulting solution was acidified with hydrochloric acid when the product emerged out on cooling. This was crystallised using methanol as solvent, filtered, dried and weighed 3.85 g (61%), m.p. 158°.

Anal. for $C_{17}H_{13}O_4$

Calcd: C, 69.14; H, 4.44; N, 4.74.

Found: C, 69.10; H, 4.41; N, 4.66.

17. Synthesis of α-N-Benzoylamino-β-indolylacrylic acid

2-Phenyl-4-(3'-indolylmethylene)-5-oxazolone (5 g) was suspended in sodium hydroxide solution (20 ml, 15%). This was heated at reflux temperature for 20 min. The solution was acidified with hydrochloric acid when on cooling a crystalline mass was obtained. This was recrystallised using methanol and filtered when it weighed 3.95 g (66%), m.p. 239°.

Anal. for $C_{18}H_{14}O_3N_2$

Calcd: C, 70.58; H, 4.57; N, 9.15.

Found: C, 70.56; H, 4.55; N, 9.10.

(b) Synthesis of N-Benzoylaminoacryloyl chloride

1. Synthesis of α-N-Benzoylamino-β-(p-methoxyphenyl) acryloyl chloride

A mixture of α-N-Benzoylamino-β-(p-methoxyphenyl) acrylic acid (2.9 g; 0.1 mol) and phosphorous pentachloride (2 g; 0.1 mol) was added to dry benzene (50 ml) and heated gently for 15 minutes. The solution was evaporated to dryness under reduced pressure on a steam bath and the product so secured was crystallised from benzene. This was filtered, dried and weighed 2.07 g (66%), m.p. 144°.

Anal. for $C_{17}H_{14}O_3NCl$

Calcd: C, 64.65; H, 4.43; N, 4.43.

Found: C, 64.66; H, 4.42; N, 4.44.

2. Synthesis of α-N-Benzoylamino-β-(3'-methoxy-4'-hydroxyphenyl)acryloyl chloride

α-N-Benzoylamino-β-(3'-methoxy-4'-hydroxyphenyl)acrylic acid (3.7 g; 0.1 mol) and phosphorous pentachloride (2 g; 0.1 mol) was heated with dry benzene (50 ml) for 15 min. This was evaporated to dryness under diminished pressure. The product was crystallised from benzene and filtered, when on drying, it weighed 2.08 g (63%), m.p. 198°.

Anal. for $C_{17}H_{12}O_4NCl$

Calcd: C, 61.91; H, 3.64; N, 4.24.

Found: C, 61.88; H, 3.60; N, 4.21.

3. Synthesis of α-N-Benzoylamino-β-cinnamylacryloyl chloride

α-N-Benzoylamino-β-cinnamylacrylic acid (2.9 g; 0.1 mol), phosphorous pentachloride (2.09 g; 0.1 mol) and dry benzene (50 ml) was gently heated for 15 min. The solvent was evaporated to dryness under reduced pressure. The product was crystallised using benzene as solvent. This was filtered, dried and weighed 1.80 g (59%), m.p. 188°.

Anal. for $C_{18}H_{14}O_2NCl$

Calcd: C, 69.34; H, 4.49; N, 4.50.

Found: C, 69.32; H, 4.46; N, 4.44.

4. Synthesis of α-N-benzoylamino-β-(o-methoxyphenyl) acryloyl chloride

An intimate mixture of α-N-benzoylamino-β-(o-methoxyphenyl)acrylic acid (3 g; 0.1 mol), phosphorous pentachloride (2 g; 0.1 mol) was heated with dry benzene (50 ml) for 15 min. This was evaporated to dryness under diminished pressure. The residue was crystallised through benzene. This was filtered, dried and weighed 1.44 g (46 %), m.p. 195°.

Anal. for $C_{17}H_{14}O_3NCl$

Calcd: C, 64.65; H, 4.43; N, 4.43.

Found: C, 64.66; H, 4.45; N, 4.45.

5. Synthesis of α-N-benzoylamino-β-(p-hydroxyphenyl) acryloyl chloride

In dry benzene (50 ml), α-N-benzoyl-β-(p-hydroxyphenyl) acrylic acid (2.9 g; 0.1 mol) and phosphorous pentachloride (2 g; 0.1 mol) were added. This was heated for 15 min. The solvent was evaporated under reduced pressure to dryness. The residue was crystallised from benzene. This was filtered, dried and weighed 1.68 g (56 %), m.p. 136°.

Anal. for $C_{16}H_{12}O_3NCl$

Calcd: C, 63.68; H, 3.98; N, 4.64.

Found: C, 63.64; H, 3.88; N, 4.58.

6. Synthesis of α-N-Benzoyl-β-(p-dimethylaminophenyl) acryloyl chloride

An intimate mixture of α-N-benzoyl-β-(p-dimethylamino-phenyl)acrylic acid (3.1 g; 0.1 mol) phosphorous pentachloride (2.0 g; 0.1 mol) was heated with dry benzene (30 ml) for 15 min. The solvent was reduced under diminished pressure, this was then crystallised from benzene, filtered, dried when it weighed 1.57 g (48%), m.p. 166°.

Anal. for $C_{18}H_{17}O_2N_2Cl$

Calcd: C, 65.75; H, 5.17; N, 8.52.

Found: C, 65.70; H, 5.14; N, 8.50.

7. Synthesis of α-N-Benzoylamino-β-(3',4'-dimethoxyphenyl) acryloyl chloride

α-N-Benzoylamino-β-(3',4'-dimethoxyphenyl)acrylic acid (3.2 g; 0.1 mol) was suspended in dry benzene (30 ml) along with phosphorous pentachloride (2 g; 0.1 mol), this was heated for 15 min. The solvent was evaporated under reduced pressure and the residue so secured was dissolved in benzene. On cooling the product emerged out in crystalline form. Yield 1.79 g (52%), m.p. 144°.

Anal. for $C_{19}H_{16}O_4NCl$

Calcd: C, 62.51; H, 4.63; N, 4.05.

Found: C, 62.50; H, 4.65; N, 4.0.

8. Synthesis of α-N-Benzoylamino-β-(2',4'-dihydroxyphenyl) acryloyl chloride

A mixture of α-N-benzoylamino-β-(2',4'-dihydroxyphenyl) acrylic acid (2.9 g; 0.1 mol), phosphorous pentachloride (2 g; 0.1 mol) was heated in dry benzene (50 ml) for 15 min. The solvent was evaporated under diminished pressure. This was crystallised using benzene as solvent. The product thus obtained was filtered, dried when it weighed 1.68 g (54%), m.p. 132°.

Anal. for $C_{16}H_{12}O_4NCl$

Calcd: C, 60.47; H, 3.77; N, 4.40.

Found: C, 60.45; H, 3.68; N, 4.36.

9. Synthesis of α-N-Benzoylamino-β-furfurylacryloyl chloride

α-N-Benzoylamino-β-furfurylacrylic acid (2.5 g; 0.1 mol) and phosphorous pentachloride (2 g; 0.1 mol) was heated with dry benzene (50 ml) for 15 min. This was evaporated under reduced pressure. The residue thus obtained was crystallised using benzene as solvent. The crystalline material was filtered, dried and weighed 1.78 g (65%), m.p. 153°.

Anal. for $C_{14}H_{10}O_3NCl$

Calcd: C, 60.98; H, 3.62; N, 5.08.

Found: C, 60.88; H, 3.60; N. 4.89.

10. Synthesis of α-N-Benzoylamino-β-(1'-napthyl) acryloyl chloride

A mixture of α-N-benzoylamino-β-(1'-napthyl)acrylic acid (3.1 g; 0.1 mol), phosphorous pentachloride (2.0 g; 0.1 mol) was heated with dry benzene (50 ml) for 15 min. This was evaporated to dryness under reduced pressure. The residue was then crystallised through benzene which was filtered and dried. Yield 1.83 g (56%), m.p. 170°.

Anal. for $C_{20}H_{14}O_2NCl$

Calcd: C, 71.50; H, 4.17; N, 4.17.

Found: C, 71.48; H, 4.0 ; N, 4.21.

11. Synthesis of α-N-Benzoylamino-β-isopropylacryloyl chloride

α-N-Benzoylamino-β-isopropylacrylic acid (2.1 g; 0.1 mol), phosphorous pentachloride (2 g; 0.1 mol) was heated with dry benzene (50 ml) for 15 min. This was evaporated to dryness under diminished pressure. The crystalline product thus obtained using benzene as a solvent, which was filtered dried and weighed 1.46 g (62%), m.p. 108°.

Anal. for $C_{12}H_{12}O_2NCl$

Calcd: C, 60.63; H, 5.05; N, 5.89.

Found: C, 60.61; H, 5.0 ; N, 5.86.

12. Synthesis of α-N-Benzoylamino-β-cyclohexylacryloyl chloride

An intimate mixture of α-N-benzoylamino-β-cyclohexylacrylic acid (2.7 g; 0.1 mol), phosphorous pentachloride (2 g; 0.1 mol) was dissolved in dry benzene (50 ml). This was gently heated for 15 min. The crude product obtained by evaporating the solvent under reduced pressure was crystallised through benzene. This was filtered and dried. Yield 1.38 g (48%), m.p. 156°.

Anal. for $C_{16}H_{16}O_2NCl$

Calcd: C, 66.32; H, 5.52; N, 4.83.

Found: C, 66.30; H, 5.48; N, 4.78.

13. Synthesis of α-N-Benzoylamino-β-phenylacryloyl chloride

A mixture of α-N-benzoylamino-β-phenylacrylic acid (2.6 g; 0.1 mol) and phosphorous pentachloride (2 g; 0.1 mol) were heated in dry benzene (50 ml) for 15 min. Solvent was then evaporated under reduced pressure. The crystalline mass thus obtained was filtered, dried and weighed 1.99 g (70%), m.p. 130°.

Anal.for $C_{16}H_{12}O_2NCl$

Calcd: C, 67.25; H, 4.20; N, 4.90.

Found: C, 67.21; H, 4.18; N, 4.96.

14. Synthesis of α-N-Benzoylamino-β-(o-hydroxyphenyl) acryloyl chloride

α-N-Benzoylamino-β-(o-hydroxyphenyl)acrylic acid (2.8 g; 0.1 mol) and phosphorous pentachloride (2 g ; 0.1 mol) was gently heated with dry benzene (50 ml) for 15 min. This was evaporated to dryness under diminished pressure. The product was crystallised using benzene. This was filtered, dried and weighed 2.04 g (68 %), m.p. 174°.

Anal. for $C_{16}H_{12}O_3NCl$

Calcd: C, 63.68; H, 3.98; N, 4.64.

Found: C, 63.65; H, 3.98; N, 4.38.

15. Synthesis of α-N-Benzoylamino-β-crotonylacryloyl chloride

An intimate mixture of α-N-benzoylamino-β-crotonyl-acrylic acid (2.5 g; 0.1 mol), phosphorous pentachloride (2 g; 0.1 mol) and dry benzene (50 ml) was heated for 15 min. The solvent was removed under reduced pressure. The crystalline mass thus obtained was crystallised using benzene. This was filtered, dried and weighed 1.64 g (58 %), m.p. 159°.

Anal. for $C_{15}H_{12}O_2NCl$

Calcd: C, 65.81; H, 4.38; N, 5.11.

Found: C, 65.80; H, 4.36; N, 5.09.

16. Synthesis of α-N-Benzoylamino-β-piperonylacryloyl chloride

α-N-Benzoylamino-β-piperonylacrylic acid (2.9 g; 0.1 mol), and phosphorous pentachloride (2 g; 0.1 mol) was heated with dry benzene (50 ml) for 15 min. This was evaporated to dryness under diminished pressure. The crystallised product thus obtained from benzene was filtered and dried. Yield 1.31 g (42%), m.p. 132°.

Anal. for $C_{17}H_{12}O_3NCl$

Calcd: C, 65.07; H, 3.82; N, 4.46.

Found: C, 65.0 ; H, 3.78; N, 4.44.

17. Synthesis of α-N-Benzoylamino-β-indolylacryloyl chloride

A mixture of α-N-benzoylamino-β-indolylacrylic acid (3.0 g; 0.1 mol), phosphorous pentachloride (2 g; 0.1 mol) was heated with dry benzene (50 ml) for 15 min. The solvent was evaporated to dryness under reduced pressure the residue so secured was crystallised from benzene. This was filtered, dried and weighed 1.70 g (62%), m.p. 153°.

Anal. for $C_{18}H_{13}O_2N_2Cl$

Calcd: C, 60.0; H, 3.61; N, 7.77.

Found: C, 59.69; H, 3.54; N, 7.67.

(c) Synthesis of 3-substituted Pyruvic acid

1. Synthesis of 3-N-Benzoylamino-3-(p-methoxybenzal)pyruvic acid

α-N-benzoylamino-β-(p-methoxyphenyl)acryloyl chloride (2.97 g; 0.1 mol) was added in aqueous potassium cyanide solution (10%, 20 ml). This was heated at reflux temperature for 20 hr. When a clear solution was obtained, heating was stopped and the solution was acidified using hydrochloric acid (20%). The solution was again heated for 15 min. On cooling 3-substituted pyruvic acid separated, which was recrystallised from ethanol. This was filtered, dried when it weighed 1.56 g (48%), m.p. 206°; UV λ_{max}^{MeOH} 230 and 305 nm; IR (Nujol) 3225, 1740, 1690, 1650, 1600, 1510, 1460, 1375, 1320, 1250 cm^{-1}; NMR (CCl_4) 9.6, 8.6, 8.2, 6.4, 2.4 δ.

Anal. for $C_{18}H_{15}O_5N$

Calcd: C, 66.45; H, 4.65; N, 4.31.

Found: C, 66.39; H, 4.63; N, 4.30.

3. Synthesis of 3-N-Benzoylamino-3-(3'-methoxy-4'-hydroxybenzal) pyruvic acid

α-N-benzoylamino-β-(3'-methoxy-4'-hydroxyphenyl)acryloyl chloride (3.29 g; 0.1 mol) was taken in aqueous potassium cyanide (10%, 20 ml). This was heated at reflux temperature for 18 hr. After cooling the solution was acidified with hydrochloric acid (30%). This was again heated for 15 min. The product thus

obtained was crystallised from ethanol. This was filtered and dried. Yield 1.41 g (43%), m.p. 178°; UV λ_{max}^{MeOH} 220 nm; IR (Nujol) 3290, 2650, 1750, 1720, 1680, 1620, 1540, 1470, 1340, 1260 cm^{-1}; NMR (CCl_4) 9.5, 8.4, 7.8, 6.8, 6.4, 2.4 δ.

Anal. for $C_{19}H_{15}O_6N$

Calcd: C, 63.34; H, 4.43; N, 4.10.

Found: C, 63.30; H, 4.40; N, 4.11.

3. Synthesis of 3-N-Benzoylamino-3-cinnamylidene pyruvic acid

α-N-Benzoylamino-β-cinnamylacryloyl chloride (3.11 g; 0.1 mol) dissolved in aqueous potassium cyanide solution (10%, 20 ml) was refluxed for 20 hr resulting in a clear solution. Then it was acidified using hydrochloric acid (20%) and further heated for 20 min. On cooling the product emerged out. This was recrystallised using ethanol, filtered, dried and weighed 1.21 g (39%), m.p. 225°; UV λ_{max}^{MeOH} 223 nm; IR (Nujol) 3253, 1760, 1710, 1640, 1620, 1595, 1540, 1372, 1280 cm^{-1}; NMR (CCl_4) 9.4, 8.6, 7.4, 6.6 δ.

Anal. for $C_{19}H_{15}O_4N$

Calcd: C, 71.02; H, 4.71; N, 4.36

Found: C, 71.0 ; H, 4.70; N, 4.29.

4. Synthesis of 3-N-Benzoylamino-3-(o-methoxybenzal)pyruvic acid

α-N-Benzoylamino-β-(o-methoxyphenyl)acryloyl chloride (3.15 g; 0.1 mol) was added to an aqueous solution of potassium cyanide (10%, 20 ml). This was heated at reflux temperature. Hydrochloric acid was then added to the clear solution and again heated for 18 min. The product obtained on cooling was crystallised using ethanol. This was filtered, dried and weighed 1.75 g (54%), m.p. 201-2°; UV λ_{max}^{MeOH} 230, 280 nm; IR (Nujol) 3260, 1750, 1730, 1650, 1610, 1480, 1390, 1240 cm^{-1}; NMR (CCl_4) 9.2, 9.4, 7.9, 6.6, 2.4 δ.

Anal. for $C_{19}H_{15}O_5N$

Calcd: C, 66.45; H, 4.65; N, 4.31

Found: C, 66.30; H, 4.50; N, 4.29.

5. Synthesis of 3-N-Benzoylamino-3-(p-hydroxybenzal)pyruvic acid

α-N-Benzoylamino-β-(p-hydroxyphenyl)acryloyl chloride (3 g; 0.1 mol) was dissolved in aqueous potassium cyanide solution (10%; 20 ml). This was heated at reflux temperature. To this clear solution hydrochloric acid (20%) was added in a minimum quantity. This was again heated for 20 min. The residue so secured on cooling was crystallised through ethanol which was filtered, dried and weighed 1.08 g (36%), m.p. 220°; UV λ_{max}^{MeOH} 220, 240 nm; IR (Nujol) 3200, 2715, 1760, 1665, 1602,

1570, 1510, 1460, 1380, 1275, 1220 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 7.8, 6.6, 6.2 δ.

Anal. for $C_{17}H_{13}O_5N$

Calcd: C, 65.59; H, 4.21; N, 4.50.

Found: C, 65.58; H, 4.19; N, 4.50.

6. Synthesis of 3-N-Benzoylamino-3-(p-dimethylaminobenzal) pyruvic acid

To an aqueous solution of potassium cyanide (20 ml; 10%), α-N-benzoylamino-β-(p-dimethylaminophenyl)acryloyl chloride (3.5 g; 0.1 mol) was added, this was heated at reflux temperature for 18 hr, then it was acidified using hydrochloric acid (20%) and again heated for 20 min. The product thus obtained was crystallised using ethanol, filtered, dried and weighed 1.28 g (38%), m.p. 158°; UV λ_{max}^{MeOH} 230, 260 nm; IR (Nujol) 3280, 2710, 1725, 1720, 1680, 1640, 1570, 1530, 1480, 1360, 1240 cm^{-1}; NMR (CCl_4) 9.2, 8.6, 8.4, 7.8, 6.6 δ.

Anal. for $C_{19}H_{17}O_4N_2$

Calcd: C, 67.60; H, 5.0; N, 8.31.

Found: C, 67.60; H, 4.90; N, 8.30.

7. Synthesis of 3-N-Benzoylamino-3-(3',4'-dimethoxybenzal) pyruvic acid

α-N-Benzoylamino-β-(3',4'-dimethoxyphenyl)acryloyl chloride (3.55 g; 0.1 mol) was heated at reflux temperature with aqueous potassium cyanide solution (10%, 20 ml) for 20 hr. The solution was then acidified with hydrochloric acid (20%). This was again heated for 15 min. The product was crystallised through ethanol. This was filtered, dried and weighed 2.27 g (64%), m.p. 190°; UV λ_{max}^{MeOH} 230, 255 nm; IR (Nujol) 3290, 1750, 1775, 1710, 1680, 1640, 1610, 1500, 1460, 1370, 1280 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 7.8, 6.6, 3.4 δ.

Anal. for $C_{19}H_{17}O_6N$

Calcd: C, 64.22; H, 4.82; N, 3.94.

Found: C, 64.20; H, 4.79; N, 3.89.

9. Synthesis of 3-N-Benzoylamino-3-(2',4'-dihydroxybenzal) pyruvic acid

α-N-Benzoylamino-β-(2',4'-dihydroxyphenyl)acryloyl chloride (3.19 g; 0.1 mol) was suspended in aqueous potassium cyanide solution (10%; 20 ml) and was gently heated to reflux temperature for 22 hr. This was acidified using hydrochloric acid (20%) and again heated for 20 min. The residue obtained was crystallised using ethanol. This was filtered and dried when it melted at 160° and weighed 1.40 g (44%); UV λ_{max}^{MeOH} 220,

240 nm; IR (Nujol) 3300, 2710, 3115, 1780, 1740, 1660, 1620, 1540, 1480, 1370, 1260 cm^{-1}; NMR (CCl_4) 9.2, 8.6, 7.4, 6.4, 6.2 δ.

Anal. for $C_{17}H_{13}O_6N$

Calcd: C, 62.38; H, 4.0; N, 4.28.

Found: C, 62.36; H, 3.98; N, 4.21.

9. Synthesis of 3-N-Benzoylamino-3-furfurylidene pyruvic acid

α-N-Benzoylamino-β-furfurylacryloyl chloride (2.75 g; 0.1 mol) was dissolved in aqueous potassium cyanide solution (10%, 20 ml). This was heated under reflux for 24 hr. The solution was then acidified with hydrochloric acid (20%) and again heated for 30 min. The product obtained on cooling was crystallised using ethanol. This was filtered and weighed 1.56 g (57%) and melted at 210°; UV λ_{max}^{MeOH} 240, 280 nm; IR (Nujol) 3380, 3360, 1940, 1780, 1670, 1640, 1580, 1550, 1501, 1450, 1370, 1270 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 8.4, 7.8, 6.6, 6.3 δ.

Anal. for $C_{15}H_{11}O_5N$

Calcd: C, 63.16; H, 3.89; N, 4.91.

Found: C, 63.11; H, 3.88; N, 4.90.

10. Synthesis of 3-N-Benzoylamino-3-(1'-napthylidene) pyruvic acid

α-N-Benzoylamino-β-(1-napthyl)acryloyl chloride (3.35 g; 0.1 mol) was gently heated under reflux with aqueous potassium cyanide solution (10%; 20 ml) for 25 hr. The solution was then acidified with hydrochloric acid (20%). This was heated again for 18 min., residue thus obtained was filtered and crystallised using ethanol. This was filtered and dried. Yield 1.40 g (42%), m.p. 217-18°; UV λ_{max}^{MeOH} 230, 280 nm; IR (Nujol) 3270, 2180, 1785, 1740, 1680, 1540, 1470, 1360, 1340, 1275, 1240 cm^{-1}; NMR (CCl_4) 9.4, 8.6, 7.8, 6.6, 6.2 δ.

Anal. for $C_{21}H_{15}O_4N$

Calcd: C, 73.03; H, 4.38; N, 4.06.

Found: C, 73.01; H, 4.40; N, 4.0.

11. Synthesis of 3-N-Benzoylamino-3-isopropylidene pyruvic acid

Powdered α-N-benzoylamino-β-isopropylacryloyl chloride (2.38 g; 0.1 mol) was taken in aqueous potassium cyanide solution (10%; 20 ml). This was heated at reflux temperature for 22 hr. The solvent was acidified with hydrochloric acid (20%) and again heated for 20 min. The product thus obtained was crystallised using ethanol, filtered, dried and weighed 0.86 g (36%), m.p. 126°; UV λ_{max}^{MeOH} 230 nm; IR (Nujol) 3270, 2140, 1760, 1700, 1680, 1640, 1590, 1510, 1420, 1380, 1240 cm^{-1}; NMR (CCl_4) 9.0, 8.4, 8.2, 7.8, 6.6 δ.

Anal. for $C_{13}H_{13}O_4N$

Calcd: C, 63.15; H, 5.30; N, 5.67.

Found: C, 63.12; H, 5.28; N, 5.55.

12. Synthesis of 3-N-Benzoylamino-3-cyclohexylidene pyruvic acid

α-N-Benzoylamino-β-cyclohexylacryloyl chloride (2.90 g; 0.1 mol) was dissolved in aqueous potassium cyanide solution (10%, 20 ml), and was refluxed for 30 hr. Clear solution thus obtained was then acidified using hydrochloric acid (20%) and this was again heated for 18 min. The crude product obtained on cooling was crystallised from ethanol. This was filtered, dried and weighed 0.87 g (30%); m.p. 198°; UV λ_{max}^{MeOH} 240 nm; IR (Nujol) 3290, 2110, 1770, 1740, 1670, 1630, 1540, 1480, 1390, 1320, 1280, 1240 cm^{-1}; NMR (CCl_4) 9.4, 8.8, 8.4, 7.8, 6.8, 6.4 δ.

Anal. for $C_{16}H_{17}O_4N$

Calcd: C, 66.88; H, 5.96; N, 4.88.

Found: C, 66.86; H, 5.88; N, 4.80.

13. Synthesis of 3-N-Benzoylamino-3-benzal pyruvic acid

α-N-Benzoylamino-β-phenylacryloyl chloride (2.85 g; 0.1 mol) was added to aqueous potassium cyanide solution (10%; 30 ml). This was refluxed for 20 hr. The clear solution thus obtained was acidified with hydrochloric acid (20%) and again heated for 15 min. On cooling the product obtained was

crystallised using ethanol. This was filtered, dried when it weighed 1.76 g (62) and melted at 251-52°; UV λ_{max}^{MeOH} 330, 280 nm; IR (Nujol) 3300, 2650, 1785, 1680, 1635, 1598, 1572 cm^{-1}; NMR (CCl_4) 9.7, 8.4, 8.2, 6.9 δ.

Anal. for $C_{17}H_{13}O_4N$

Calcd: C, 69.14; H, 4.40; N, 4.74.

Found: C, 69.01; H, 4.33; N, 4.74.

14. Synthesis of 3-N-Benzoylamino-3-(o-hydroxybensal) pyruvic acid

Powdered α-N-benzoylamino-β-(o-hydroxyphenyl)acryloyl chloride (3.0 g; 0.1 mol) was refluxed with aqueous potassium cyanide solution (10%; 20 ml) for 20 hr. The clear solution obtained was acidified with hydrochloric acid (20%) and again heated for 15 min. After cooling the product obtained was crystallised from ethanol. This was filtered, dried and weighed 1.08 g (36%), m.p. 114-15°; UV λ_{max}^{MeOH} 230, 260 nm; IR (Nujol) 3300, 2720, 1760, 1700, 1660, 1590, 1520, 1440, 1360, 1340, 1290 cm^{-1}; NMR (CCl_4) 9.4, 8.6, 8.4, 7.4, 6.6 δ.

Anal. for $C_{17}H_{13}O_5N$

Calcd: C, 65.59; H, 4.21; N, 4.50.

Found: C, 65.58; H, 4.19; N, 4.50.

15. Synthesis of 3-N-Benzoylamino-3-crotonylidene pyruvic acid

α-N-Benzoylamino-β-crotonylacryloyl chloride (2.74 g; 0.1 mol) was suspended in aqueous potassium cyanide solution (10%; 20 ml). This was gently heated for 20 hr. then acidified with hydrochloric acid (20%) and heated again for 15 min. On cooling crystalline product was obtained which was recrystallised using ethanol. This was filtered and dried. Yield 0.93 g (34%) m.p. 192°; UV λ_{max}^{MeOH} 230, 240 nm; IR (Nujol) 3290, 2170, 1760, 1720, 1640, 1610, 1570, 1480, 1420, 1370, 1280, 1260 cm^{-1}; NMR (CCl_4) 9.2, 8.6, 8.4, 7.4, 6.6 δ.

Anal. for $C_{14}H_{13}O_4N$

Calcd: C, 64.86; H, 5.05; N, 5.40.

Found: C, 64.94; H, 5.00; N, 5.34.

16. Synthesis of 3-Benzoylamino-3-piperonylidene pyruvic acid

α-N-Benzoylamino-β-piperonylacryloyl chloride (3.14 g; 0.1 mol) was heated at reflux temperature with aqueous potassium cyanide solution for 24 hr. To this hydrochloric acid (20%) was added and the solution was again heated for 20 min. On cooling the product emerged out in crystalline form. This was recrystallised using ethanol and filtered. The dried product melts at 179° and weighed 1.88 g (60%); UV λ_{max}^{MeOH} 230, 265 nm; IR (Nujol) 3290, 2740, 1770, 1710, 1680, 1640, 1510, 1460, 1370,

1250 cm^{-1}; NMR (CCl_4) 9.4, 8.4, 7.8, 6.8, 6.2, 4.4 δ.

Anal. for $C_{18}H_{13}O_5N$

Calcd: C, 66.87; H, 4.05; N, 4.33.

Found: C, 66.95; H, 4.02; N, 4.31.

17. Synthesis of 3-N-Benzoylamino-3-indolylidene pyruvic acid

α-N-Benzoylamino-β-indolylacryloyl chloride (3.60 g; 0.1 mol) was suspended in aqueous potassium cyanide solution (10%; 20 ml). This was heated at reflux temperature till a clear solution was obtained. The solution was acidified using hydrochloric acid (20%) and was again heated for 20 min., ethanol was then added to the residue when a crystalline mass emerged out. This was filtered, dried and weighed 1.87 g (52%), m.p. 240°; UV λ_{max}^{MeOH} 230, 280 nm; IR (Nujol) 3290, 1780, 1740, 1690, 1620, 1570, 1540, 1480, 1360, 1240 cm^{-1}; NMR (CCl_4) 9.2, 8.6, 8.2, 7.4, 6.2 δ.

Anal. for $C_{19}H_{14}O_4N_2$

Calcd: C, 68.25; H, 4.22; N, 8.38.

Found: C, 68.24; H, 4.19; N, 8.36.

III PALLADIUM CHARCOAL (10 % Pd) CATALYSED REDUCTION*

Synthesis of α-Amino-β-N-benzoylamino acids

1. Synthesis of DL-α-Amino-β-N-benzoylamino-(p-methoxyphenyl) butyric acid

Powdered 3-N-benzoylamino-3-(p-methoxybenzal)pyruvic acid (3.25 g; 0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml, Sp. gr. 0.99) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 39 psi for 10 hr. when there was no more absorption of hydrogen, the flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was evaporated to dryness under reduced pressure and the residue was crystallised from ethanol (95%). The crystalline product thus obtained was filtered and dried when it weighed 2.65 g (81 %) and melted at 142°; UV λ_{max}^{MeOH} 227 and 275 nm; IR (Nujol) 3310, 1720, 1645, 1615, 1590, 1520, 1455, 1378, 1320, 1260 cm^{-1}.

Anal. for $C_{19}H_{20}O_4N_2$

Calcd: C, 65.94; H, 6.14; N, 8.33.

Found: C, 65.91; H, 6.08; N, 8.31.

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* All reductions were conducted in a Paar catalytic hydrogenation apparatus.

2. Synthesis of DL-α-Amino-β-N-benzoylamino-(3'-methoxy-4'-hydroxy)butyric acid

Powdered 3-N-benzoylamino-3-(3'-methoxy-4'-hydroxybenzal) pyruvic acid (3.41 g; 0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml, Sp. gr. 0.99) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 42 psi for 18 hr. After the completion of reduction the flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was dried under reduced pressure and the residue was crystallised from ethanol (95%). The product so obtained melted at 202° and weighed 3.0 g (88%); UV λ_{max}^{MeOH} 225, 280 nm; IR (Nujol) 3280, 1710, 1640, 1605, 1590, 1510, 1460, 1370, 1310, 1290, 1210 cm^{-1}.

Anal. for $C_{18}H_{20}O_5N_2$

Calcd: C, 62.78; H, 5.80; N, 8.14.

Found: C, 62.76; H, 5.74; N, 8.0.

3. Synthesis of DL-α-Amino-β-N-benzoylaminophenylhexanoic acid

Powdered 3-N-benzoylamino-3-cinnamylidenepyruvic acid (3.21 g; 0.1 mol) was suspended in 50 ml of ethanol. To this palladium charcoal (0.5 g) was added along with 10 ml of concentrated ammonia solution (Sp. gr. 0.99). This was reduced under a hydrogen pressure of 45 psi in a Paar catalytic hydrogenation apparatus

for 14 hr. The flask was disconnected, contents heated on a steam bath to dissolve the product and filtered hot. The catalyst was washed with three 20 ml portions of boiling ethanol. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue so secured was crystallised from ethanol (95%). The crystalline material thus obtained was filtered and dried, yield 2.65 g (88%), m.p. 165°; UV λ_{max}^{MeOH} 220 m
IR (Nujol) 3255, 1688, 1640, 1625, 1600, 1585, 1505, 1372, 1280, 1250 cm^{-1}.

Anal. for $C_{19}H_{20}O_3N_2$

Calcd: C, 70.35; H, 6.22; N, 8.64.

Found: C, 70.34; H, 6.10; N, 8.62.

4. <u>Synthesis of DL-α-Amino-β-N-benzoylamino-(o-methoxyphenyl) butyric acid</u>

Powdered 3-N-benzoylamino-3-(o-methoxybenzal)pyruvic acid (3.25 g; 0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml, Sp gr 0.99) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 38 psi. After 16 hr when there was no more absorption of hydrogen, the flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was evaporated to dryness under reduced pressure and the residue was crystallised from ethanol (95%). The amide thus obtained melted at 170° and weighed

2.75 g (94%). UV λ_{max}^{MeOH} 235 nm; IR (Nujol) 3325, 1722, 1610, 1600, 1570, 1535, 1490, 1378, 1358, 1340, 1270, 1230 cm^{-1}.

Anal. for $C_{18}H_{20}O_4N$

Calcd: C, 65.84; H, 6.14; N, 8.53.

Found: C, 65.85; H, 6.19; N, 8.51.

5. Synthesis of DL-α-Amino-β-N-benzoylamino-(o-hydroxyphenyl) butyric acid

Powdered 3-N-benzoylamino-3-(p-hydroxybenzal)pyruvic acid (3.11 g; 0.1 mol) was suspended in 30 ml of ethanol followed by the addition of ammonia solution (10 ml, Sp gr. 0.99) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 48 psi. The reduction was complete in 15 hr. The flask was disconnected, contents heated on a steam bath and filtered hot. The catalyst was washed with three 30 ml portions of boiling ethanol. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue was crystallised from ethanol (95%). The crystalline acid thus obtained on drying weighed 2.35 g (75%) and melted at 174°; UV λ_{max}^{MeOH} 220, 280 nm; IR (Nujol) 3190, 1680, 1640, 1570, 1510, 1460, 1320, 1270 cm^{-1}.

Anal. for $C_{17}H_{18}O_4N_2$

Calcd: C, 64.95; H, 5.77; N, 8.91.

Found: C, 64.88; H, 5.72; N, 8.87.

6. Synthesis of DL-α-Amino-β-N-benzoylamino-(p-dimethylamino-phenyl) butyric acid

Powdered 3-N-benzoylamino-3-(p-dimethylaminobenzal) pyruvic acid (3.37 g; 0.1 mol) was suspended in 50 ml of ethanol. To this palladium charcoal (0.5 g) was added along with ammonia solution (10 ml, Sp gr. 0.99). This was reduced under a hydrogen pressure of 55 psi for 14 hr. when there was no more absorption of hydrogen, the flask was disconnected, contents boiled on a steam bath and filtered hot. The catalyst was washed on the Buchner funnel thrice with 10 ml portions of warm ethanol. The filtrate and washings were evaporated to dryness under reduced pressure, the residue thus obtained was dissolved in minimum amount (10 ml) of ethanol (95%) and left for crystallisation. The crystalline product was filtered, dried and weighed 2.38 g (70%), m.p. 115°; UV λ_{max}^{MeOH} 225, 310 nm; IR (*Nujol*) 3310, 1690, 1640, 1570, 1540, 1480, 1420, 1360, 1240 cm^{-1}.

Anal. for $C_{19}H_{22}O_3N_3$

Calcd: C, 67.00; H, 6.47; N, 12.36.

Found: C, 67.10; H, 6.41; N, 12.40.

7. Synthesis of DL-α-Amino-β-N-benzoylamino-(3',4'-dimethoxy-phenyl) butyric acid

Powdered 3-N-benzoylamino-3-(3',4'-dimethoxybenzal)pyruvic acid (3.55 g; 0.1 mol) was suspended in 50 ml of ethanol

containing ammonia solution (10 ml, Sp gr. 0.99) and palladium charcoal (0.5 g). This was reduced under hydrogen pressure of 54 psi for 16 hr. After this period, the flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was evaporated to dryness under reduced pressure and the residue was crystallised from ethanol (95%). This was filtered and dried, when it weighed 3.22 g (90%) and melted at 138°; UV λ_{max}^{MeOH} 220, 320 nm; IR (Nujol) 3290, 1645, 1560, 1510, 1475, 1320, 1260 cm^{-1}.

Anal. for $C_{19}H_{22}O_5N_2$

Calcd: C, 63.67; H, 6.19; N, 7.81.

Found: C, 63.68; H, 6.12; N, 7.82.

9. Synthesis of DL-α-Amino-β-N-benzoylamino-(2',4'-dihydroxyphenyl) butyric acid

Powdered 3-N-benzoylamino-(2',4'-dihydroxybenzal)pyruvic acid (3.14 g; 0.1 mol) was suspended in ethanol (30 ml). To this palladium charcoal (0.5 g) and ammonia solution (10 ml, Sp. gr. 0.99) was added and this was reduced under a hydrogen pressure of 52 psi. The reduction was complete in 15 hr when the flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was dried under reduced pressure and the residue was crystallised from ethanol (95%). The acid so obtained melted at 146° and weighed 2.55 g (79%);

UV λ_{max}^{MeOH} 235 nm; IR (Nujol) 3270, 1720, 1680, 1640, 1640, 1575, 1460, 1370, 1290, 1240 cm^{-1}.

Anal. for $C_{17}H_{18}O_4N_2$

Calcd: C, 64.95; H, 5.77; N, 8.91.

Found: C, 64.94; H, 5.68; N, 8.86.

9. Synthesis of DL-α-Amino-β-N-benzoylaminofurfuryl butyric acid

Powdered 3-N-benzoylamino-3-furfurylidenepyruvic acid (2.85 g; 0.1 mol) was suspended in 50 ml of ethanol. To this ammonia solution (10 ml. Sp. gr. 0.99) and palladium charcoal (0.5 g) was added. This was reduced under a hydrogen pressure of 48 psi. The reduction was complete in 18 hr. The flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was dried under reduced pressure and the residue thus obtained was crystallised from ethanol (95%). The acid thus obtained on drying melted at 158° and weighed 2.47 g (96%); UV λ_{max}^{MeOH} 225, 310 nm; IR (Nujol) 3330, 1720, 1680, 1610, 1590, 1520, 1470, 1410, 1360, 1280, 1260 cm^{-1}.

Anal. for $C_{15}H_{16}O_4N_2$

Calcd: C, 62.49; H, 5.59; N, 9.72.

Found: C, 62.50; H, 5.56; N, 9.68.

10. Synthesis of DL-α-Amino-β-N-benzoylamino-(1-napthyl) butyric acid

Powdered 3-N-benzoylamino-3-(1'-napthylidene)pyruvic acid (3.45 g; 0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml Sp. gr. 0.99) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 46 psi for 16 hr. When there was no more absorption of hydrogen, the flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was dried under reduced pressure and the residue was crystallised from ethanol (95%). The crystalline product thus obtained melted at 178° and weighed 2.95 g (92%); UV λ_{max}^{MeOH} 220, 320 nm; IR (Nujol) 3270, 1680, 1640, 1610, 1580, 1520, 1470, 1420, 1370, 1290, 1260 cm^{-1}.

Anal. for $C_{21}H_{20}O_3N_2$

Calcd: C, 72.39; H, 5.79; N, 8.04.

Found: C, 72.38; H, 5.77; N, 8.0.

11. Synthesis of DL-α-Amino-β-N-benzoylaminoisopropyl butyric acid

Powdered 3-N-benzoylamino-3-isopropylidene pyruvic acid (2.47 g; 0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml Sp. gr. 0.99) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 50 psi.

The reduction was complete in 15 hr. the flask was disconnected, content heated on a steam bath and filtered hot. The filtrate was evaporated to dryness under reduced pressure and the residue was crystallised from ethanol. The crystalline product was filtered; dried and weighed 1.90 (78%) m.p. 142°; UV λ_{max}^{MeOH} 225, 275 nm; IR (Nujol) 3330, 1700, 1670, 1560, 1480, 1410, 1360, 1270, 1230 cm^{-1}.

Anal. for $C_{13}H_{18}O_3N_2$

Calcd: C, 62.39; H, 7.25; N, 11.19.

Found: C, 62.36; H, 7.30; N, 11.01.

12. Synthesis of DL- α-Amino-β-N-benzoylaminocyclohexyl butyric acid

Powdered 3-N-benzoylamino-3-cyclohexylidene pyruvic acid (2.87 g; 0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml Sp. gr. 0.99) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 48 psi. The reduction was complete in 16 hr. The flask was disconnected, contents heated on a steam bath and filtered hot. The filtrate was dried under reduced pressure and the residue was crystallised from ethanol (95%). The crystalline product on drying weighed 2.26 g (78%) and melted at 162°; UV λ_{max}^{MeOH} 215, 260 nm; IR (Nujol) 3170, 1680, 1610, 1560, 1480, 1420, 1360, 1270, 1230 cm^{-1}.

Anal. for $C_{16}H_{22}O_3N_2$

Calcd: C, 66.18; H, 7.64; N, 9.65.

Found: C, 66.16; H, 7.62; N, 9.64.

13. Synthesis of DL-α-Amino-β-N-benzoylaminophenyl butyric acid

Powdered 3-N-benzoylamino-3-benzalpyruvic acid, 2.95 g (0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml, Sp. gr. 0.99) and palladium charcoal (0.5 g). This was reduced under hydrogen pressure of 35 psi. The reduction was complete in 12 hr. The flask was disconnected, contents boiled on a steam bath and filtered hot the filtrate was dried under reduced pressure and the residue was crystallised from ethanol. The product obtained in this manner on drying melted at 165° and weighed 2.68 g (90); UV λ_{max}^{MeOH} 220 nm; IR (Nujol) 3310, 1718, 1645, 1620, 1550, 1465, 1380, 1320, 1230 cm^{-1}.

Anal. for $C_{17}H_{18}O_3N_2$

Calcd: C, 69.44; H, 6.08; N, 9.39.

Found: C, 68.30; H, 6.25; N, 9.35.

14. Synthesis of DL-α-Amino-β-N-benzoylamino-(o-hydroxyphenyl) butyric acid

Powdered 3-N-benzoylamino-3-(i-hydroxybenzal)pyruvic acid (3.11 g; 0.1 mol) was suspended in 50 ml of ethanol, palladium charcoal (0.5 g) was added along with ammonia solution (10 ml, Sp. gr. 0.99) and this was reduced under a hydrogen pressure of 48 psi. After 12 hr the reduction was complete and the flask was disconnected. The contents were heated on a steam bath and

filtered hot. The filtrate was dried under reduced pressure and the residue was crystallised from ethanol. The product weighed 2.20 g (68%), m.p. 160°; UV λ_{max}^{MeOH} 225, 320 nm; IR (Nujol) 3260, 1660, 1620, 1570, 1480, 1410, 1320, 1240 cm^{-1}.

Anal. for $C_{17}H_{18}O_4N_2$

Calcd: C, 64.95; H, 5.77; N, 8.91.

Found: C, 64.85; H, 5.69; N, 8.88.

15. Synthesis of DL-α-Amino-β-N-benzoylaminocrotonyl butyric acid

Powdered 3-N-benzoylamino-3-crotonylidenepyruvic acid (2.60 g; 0.1 mol) was suspended in 50 ml of ethanol containing ammonia solution (10 ml) and palladium charcoal (0.5 g). This was reduced under a hydrogen pressure of 60 psi for 13 hr when there was no more absorption of hydrogen, the flask was disconnected, contents heated on a steam bath and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was crystallised from ethanol (95%). The product thus obtained melted at 174° and weighed 1.93 g (74%); UV λ_{max}^{MeOH} 220, 270 nm; IR (Nujol) 3010, 1670, 1640, 1570, 1520, 1490, 1360, 1280, 1220 cm^{-1}.

Anal. for $C_{14}H_{18}O_3N_2$

Calcd: C, 64.10; H, 6.92; N, 10.68.

Found: C, 64.0 ; H, 6.86; N, 10.58.

16. Synthesis of DL-α-Amino-β-N-benzoylaminopiperonyl butyric acid

Powdered 3-N-benzoylamino-3-piperonylidenepyruvic acid (3.23 g; 0.1 mol) was suspended in 50 ml of ethanol. To this palladium charcoal (0.5 g) was added along with 10 ml of ammonia. This was reduced under a hydrogen pressure of 48 psi. The reduction was complete in 18 hr. The flask was disconnected, contents boiled on a steam bath and filtered. The filtrate was dried under reduced pressure and the residue was crystallised from ethanol. The crystalline product thus obtained weighed 2.93 g (90%) and melted at 145°; UV λ_{max}^{MeOH} 223, 305 nm; IR (Nujol) 3200, 1720, 1680, 1640, 1590, 1510, 1460, 1380, 1260 cm^{-1}.

Anal. for $C_{19}H_{20}O_4N_2$

Calcd: C, 65.94; H, 6.14; N, 8.53.

Found: C, 65.85; H, 6.08; N, 8.40.

17. Synthesis of DL-α-Amino-β-N-benzoylaminoindolyl butyric acid

Powdered 3-N-benzoylamino-3-indolylidene pyruvic acid (3.34 g; 0.1 mol) was suspended in 50 ml of ethanol along with palladium charcoal (0.5 g) and ammonia solution (10 ml). This was reduced under a hydrogen pressure of 44 psi for 18 hr. when there was no more absorption of hydrogen, the flask was

disconnected, contents boiled on a steam bath and filtered. The filtrate was dried under reduced pressure, and the residue was crystallised from ethanol (95%) the product thus obtained melted at 162° and weighed 2.90 g (90%); UV λ_{max}^{MeOH} 220, 315 nm; IR (Nujol) 3160, 1690, 1640, 1610, 1560, 1480, 1420, 1340, 1280 cm^{-1}.

Anal. for $C_{19}H_{19}O_3N_2$

Calcd: C, 73.76; H, 6.19; N, 4.53.

Found: C, 73.77; H, 6.20; N, 4.60.

IV. HYDROLYSIS OF α-AMINO-β-N-BENZOYL AMINO ACIDS

Synthesis of DL-α,β-Diamino acids

1. Synthesis of DL-α,β-Diamino-γ-(p-methoxyphenyl) butyric acid

DL-α-Amino-β-N-benzoylamino (p-methoxyphenyl)butyric acid (3.28 g; 0.1 mol) was added to 50 ml of concentrated hydrochloric acid (36%) and refluxed for 19 hr. The mixture was left overnight at room temperature. Next morning benzoic acid crystallised, this was filtered and washed with three 10 ml portions of distilled water. The filtrate and washings were combined and evaporated to dryness under reduced pressure. The residue so secured was dissolved in 25 ml of water and evaporated again. Then the residue was taken in 20 ml of water, neutralised with dilute ammonia solution and 10 ml of ethanol was added. On cooling the amino acid crystallised out. This was filtered and dried. Yield 1.56 g (70%), m.p. 215°; UV λ_{max}^{MeOH} 225, 280 nm; IR (Nujol) 3140, 2730, 1610, 1580, 1520, 1410, 1340, 1230 cm^{-1}.

Anal. for $C_{11}H_{16}O_3N_2$

Calcd: C, 58.91; H, 7.19; N, 12.49.

Found: C, 58.81; H, 7.20; N, 12.50.

2. Synthesis of DL-α,β-Diamino-γ-(3'-methoxy-4'-hydroxy) butyric acid

DL-α-Amino-β-N-benzoylamino (3'-methoxy-4'-hydroxy) butyric acid (3.44 g; 0.1 mol) was refluxed with 50 ml of concentrated hydrochloric acid (36%) for 18 hr and then left at room temperature overnight. Next morning benzoic separated was filtered and washed three times with 10 ml portions of ice cold water. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in 30 ml of water and neutralised with ammonia solution, warmed on a steam bath then 40 ml of ethanol was added and cooled when crystalline amino acid obtained was filtered, washed with ethanol and dried. It weighed 1.77 g (74 %) and melted at 220°; UV λ_{max}^{MeOH} 330 nm; IR (Nujol) 2770, 2600, 1732, 1620, 1535, 1505, 1375, 1242 cm^{-1}.

Anal. for $C_{11}H_{16}O_4N_2$

Calcd: C, 59.99; H, 6.71; N, 11.60

Found: C, 59.88; H, 6.68; N, 11.58.

3. Synthesis of DL-α,β-Diamino-ω-phenylhexanoic acid

DL-α-Amino-β-N-benzoylamino-phenylhexanoic acid (3.24g; 0.1 mol) was heated under reflux with concentrated hydrochloric acid (36%, 50 ml) for 19 hr, and left at room temperature overnight. Benzoic acid thus separated was filtered and the

filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in 25 ml of water, neutralised with dilute ammonia solution and then concentrated to 15 ml, ethanol (20 ml) was added when the amino acid crystallised out on cooling, this was filtered and dried. It weighed 1.54 g (70%) and melted at 215°; UV λ_{max}^{MeOH} 265 nm; IR (Nujol) 3030, 2710, 1610, 1570, 1400, 1380, 1335 cm^{-1}.

Anal. for $C_{12}H_{16}O_2N_2$

Calcd: C, 65.43; H, 7.32; N, 12.72.

Found: C, 65.50; H, 7.40; N, 12.68.

4. <u>Synthesis of DL-α,β-Diamino-γ-(o-methoxyphenyl) butyric acid</u>

DL-α-Amino-β-N-benzoylamino-(o-methoxyphenyl) butyric acid (3.28 g; 0.1 mol) was refluxed with concentrated hydrochloric acid (36%, 50 ml) for 21 hr. On cooling benzoic acid separated this was filtered. The filtrate was evaporated to dryness and the residue was dissolved in water (15 ml). This was neutralised with dilute ammonia solution. Ethanol (10 ml) was then added and cooled when dl-α,β-diamino-γ-(o-methoxyphenyl) butyric acid crystallised out. This was filtered and dried. Yield 1.68 g (75%), m.p. 225°; UV λ_{max}^{MeOH} 230, 280 nm; IR (Nujol) 3130, 2710, 2590, 1710, 1660, 1575, 1340 cm^{-1}.

Anal. for $C_{11}H_{16}O_3N_2$

Calcd: C, 58.91; H, 7.19; N, 12.49.

Found: C, 58.86; H, 7.0 ; N, 12.38.

5. **Synthesis of DL-α,β-Diamino-γ-(p-hydroxyphenyl) butyric acid**

DL-α-Amino-β-N-benzoylamino-(p-hydroxyphenyl)butyric acid (3.14 g; 0.1 mol) was refluxed with hydrochloric acid (36%, 50 ml) for 17 hr. and then left at room temperature overnight. Benzoic acid thus separated was removed through filtration and the filtrate was dried under reduced pressure. The residue was dissolved in 25 ml of water and then neutralised with dilute ammonia solution. This was concentrated to 10 ml, ethanol (20 ml) was then added and the solution was left for crystallisation. The amino acid thus obtained was filtered, washed with ethanol and dried when it weighed 1.47 g (70%) and melted at 210°; UV λ_{max}^{MeOH} 280 nm; IR (Nujol) 3130, 2650, 1670, 1620, 1540, 1380, 1250 cm^{-1}.

Anal. for $C_{10}H_{14}O_3N_2$

Calcd: C, 57.13; H, 6.71; N, 13.33.

Found: C, 57.09; H, 6.70; N, 13.30.

6. **Synthesis of DL-α,β-Diamino-γ-(p-dimethylaminophenyl) butyric acid**

DL-α-Amino-β-N-benzoylamino (p-dimethylaminophenyl) butyric acid (3.40 g; 0.1 mol) was hydrolysed in (60 ml) concentrated hydrochloric acid (36%) at reflux temperature for 16 hr and left at room temperature overnight. Next morning

the crystallised benzoic acid was filtered. The filtrate was evaporated to dryness and the residue was dissolved in small amount of water. This was neutralised with dilute ammonia solution and concentrated, ethanol (20 ml) was then added and the white crystalline product thus obtained was filtered, dried when it melted at 199°, yield 1.53 g (65%); UV λ_{max}^{MeOH} 260 nm; IR (Nujol) 3120, 2696, 1700, 1665, 1510, 1475, 1270 cm^{-1}.

Anal. for $C_{12}H_{18}O_2N_3$

Calcd: C, 61.0; H, 7.62; N, 17.70.

Found: C, 61.10; H, 7.60; N, 17.66.

7. <u>Synthesis of DL-α,β-Diamino-γ-(3',4'-dimethoxyphenyl) butyric acid</u>

DL-α-Amino-β-N-benzoylamino-(3',4'-dimethoxyphenyl) butyric acid (3.58 g; 0.1 mol) was refluxed with 30 ml of concentrated hydrochloric acid (36%) for 18 hr and then left at room temperature overnight. Next morning benzoic acid (m.p. 120°) separated was filtered and washed three times with 10 ml portions of ice cold water. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in 30 ml of water and neutralised with ammonia solution, warmed on a steam bath and then 30 ml of ethanol was added. This was cooled and the crystallised amino acid separated was filtered, washed with ethanol and dried.

It weighed 2.20 g (87%); UV λ_{max}^{MeOH} 230 nm; IR (Nujol) 3140, 2640, 2350, 1700, 1620, 1560, 1450, 1376 cm^{-1}.

Anal. for $C_{12}H_{18}O_4N_2$

Calcd: C, 56.68; H, 7.14; N, 11.02.

Found: C, 56.66; H, 7.10; N, 11.00.

9. <u>Synthesis of DL-α, β-Diamino-γ-(2',4'-dihydroxyphenyl) butyric acid</u>

DL-α-Amino-β-N-benzoylamino-(2',4'-dihydroxyphenyl) butyric acid (3.14 g; 0.1 mol) was heated under reflux with concentrated hydrochloric acid (36 %; 60 ml) for 18 hr and left at room temperature overnight. Benzoic acid thus separated was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 25 ml of water, neutralised with dilute ammonia solution and then concentrated to 15 ml. Ethanol (20 ml) was added when the amino acid crystallised on cooling was filtered and dried. It weighed 1.72 g (82%) and melted at 222°; UV λ_{max}^{MeOH} 270 nm; IR (Nujol) 2765, 2660, 1770, 1650, 1510, 1440, 1250 cm^{-1}.

Anal. for $C_{10}H_{14}O_3N_2$

Calcd: C, 57.13; H, 6.71; N, 13.33.

Found: C, 57.0 ; H, 6.68; N, 13.28.

9. Synthesis of DL-α,β-Diamino-γ-furfurylbutyric acid

DL-α-Amino-β-N-benzoylaminofurfuryl butyric acid (2.98 g; 0.1 mol) was added to 50 ml of barium hydroxide solution (15%) and refluxed for 24 hr. The mixture was left overnight at room temperature. Next morning benzoic acid crystallised out, this was filtered and washed with three 10 ml portions of distilled water. The filtrate and washings were combined and evaporated to dryness under reduced pressure. The residue so secured was redissolved in 25 ml of water and evaporated again. The residue was then taken in 20 ml of water neutralised cautiously with dilute sulphuric acid. The precipitate of barium sulphate was filtered, washed with water and 10 ml of ethanol was then added. On cooling the amino acid crystallised out. This was filtered and dried. Yield 1.38 g (75%), m.p. 202°; UV λ_{max}^{MeOH} 260 nm; IR (Nujol) 3100, 2710, 1720, 1610, 1560, 1470, 1360, 1240 cm^{-1}.

Anal. for $C_9H_{12}O_3N_2$

Calcd: C, 52.16; H, 6.57; N, 15.24.

Found: C, 52.20; H, 6.54; N, 15.19.

10. Synthesis of DL-α,β-Diamino-γ-(1-napthyl) butyric acid

DL-α-Amino-β-N-benzoylamino-(1-napthyl) butyric acid (3.48 g; 0.1 mol) was hydrolysed in 50 ml barium hydroxide solution (15%) at reflux temperature for 22 hr and left at

room temperature overnight. Next morning the crystallised benzoic acid was filtered. The filtrate was evaporated to dryness and the residue was dissolved in small amount of water. This was neutralised with dilute sulphuric acid. The precipitated barium sulphate was filtered and washed with three 20 ml portions of water. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue so secured was crystallised from aqueous ethanol (50%). The amino acid obtained in this manner melted at 226° and weighed 1.62 g (78%); UV λ_{max}^{MeOH} 280 nm; IR (Nujol) 3080, 2680, 1720, 1640, 1520, 1470, 1340, 1210 cm^{-1}.

Anal. for $C_{14}H_{16}O_2N_2$

Calcd: C, 63.44; H, 7.74; N, 13.45.

Found: C, 63.40; H, 7.72; N, 13.44.

11. Synthesis of DL-α,β-Diamino-γ-isopropylbutyric acid

DL-α-Amino-β-N-benzoylamino-isopropylbutyric acid (2.50 g; 0.1 mol) was refluxed with 50 ml of concentrated hydrochloric acid (36%) for 20 hr and then left at room temperature, overnight. Benzoic acid separated was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 25 ml of water, neutralised with ammonia solution and then concentrated to 15 ml. Ethanol (5 ml) was added when amino acid crystallised out on cooling, this was filtered and dried. It weighed 0.99 g (68%) and melted at 178°;

UV λ_{max}^{MeOH} 230 nm; IR (Nujol) 3010, 2690, 1720, 1670, 1580, 1460, 1340, 1220 cm^{-1}.

Anal. for $C_6H_{14}O_2N_2$

Calcd: C, 49.30; H, 9.65; N, 19.17.

Found: C, 49.20; H, 9.64; N, 19.20.

13. Synthesis of DL-α,β-Diamino-γ-Cyclohexylbutyric acid

DL-α-Amino-β-N-benzoyl-cyclohexylbutyric acid (2.90 g; 0.1 mol) was heated under reflux with concentrated hydrochloric acid (36%; 50 ml) for 16 hr and then left at room temperature overnight. Filtration of crystallised benzoic acid was effected over a Buchner funnel and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 25 ml of water. This was neutralised with ammonia solution and concentrated to 15 ml. Ethanol (30 ml) was added when the amino acid crystallised on cooling, was filtered and dried. It weighed 1.55 g (74%) and melted at 219°; UV λ_{max}^{MeOH} 230 nm; IR (Nujol) 3130, 2650, 2360, 1750, 1620, 1450, 1378 cm^{-1}.

Anal. for $C_{11}H_{19}O_2N_2$

Calcd: C, 63.83; H, 8.63; N, 13.32.

Found: C, 63.80; H, 8.62; N, 13.28.

13. Synthesis of DL-α,β-Diamino-γ-phenylbutyric acid

DL-α-Amino-β-N-benzoylaminophenylbutyric acid (2.98 g; 0.1 mol) was taken in 50 ml of concentrated hydrochloric acid (36%) refluxed for 18 hr and left at room temperature overnight. The crystallised benzoic acid was then filtered and washed with three successive 10 ml portions of water. The combined filtrate and washings were evaporated under diminished pressure, the residue was taken up in 25 ml of water and reevaporated. The product thus obtained was dissolved in 15 ml of water, and the solution treated with dilute ammonia solution to slight alkalinity. To this ethanol was added and cooled. Crystals of amino acid thus appeared were filtered and dried. Yield 1.64 g (85%), m.p. 235°; UV λ_{max}^{MeOH} 280 nm; IR (Nujol) 3140, 2720, 1625, 1590, 1420, 1370, 1250 cm^{-1}.

Anal. for $C_{10}H_{14}N_2O_2$

Calcd: C, 61.83; H, 7.27; N, 14.42.

Found: C, 62.01; H, 7.40; N, 14.24.

14. Synthesis of DL-α,β-Diamino-γ-(o-hydroxyphenyl) butyric acid

DL-α-Amino-β-N-benzoylamino (o-hydroxyphenyl) butyric acid (3.14 g; 0.1 mol) was refluxed with dilute hydrochloric acid (36%; 50 ml) for 15 hr and then left at room temperature overnight. Benzoic acid thus separated was filtered, washed

with three 10 ml portions of water and the combined filtrate and washings was evaporated to dryness under reduced pressure. The amino acid salt so secured was dissolved in 25 ml of water, neutralised with dilute ammonia solution, concentrated to 10 ml on a steam bath and then 30 ml of ethanol was added. The solution was cooled overnight and the crystalline amino acid separated was filtered, washed with ethanol and dried in an oven at 80° when it weighed 1.68 g (80%), m.p. 185°; UV λ_{max}^{MeOH} 230, 260 nm; IR (Nujol) 3130, 2710, 1700, 1640, 1560, 1420, 1370, 1250 cm^{-1}.

Anal. for $C_{10}H_{14}O_3N_2$

Calcd: C, 57.13; H, 7.32; N, 12.72.

Found: C, 57.0 ; H, 7.22; N, 12.69.

15. Synthesis of DL-α,β-Diamino-γ-Crotonylbutyric acid

DL-α-Amino-β-N-benzoylaminocrotonylbutyric acid (2.62 g; 0.1 mol) was hydrolysed with hydrochloric acid (36%; 50 ml) at reflux temperature for 16 hr and left at room temperature overnight. Next morning the crystallised benzoic acid was filtered. The filtrate was evaporated to dryness and the residue was dissolved in small amount of water, neutralised with dilute ammonia solution, concentrated and ethanol (20 ml) was added. The white crystallised product thus obtained was filtered, dried, when it melted at 210° and weighed 1.10 g (70%); UV λ_{max}^{MeOH} 230 nm;

IR (Nujol) 3100, 2670, 1720, 1640, 1560, 1420, 1340, 1260 cm^{-1}.

Anal. for $C_7H_{14}O_2N_2$

Calcd: C, 53.14; H, 8.92; N, 17.71.

Found: C, 53.11; H, 8.87; N, 11.66.

16. Synthesis of DL-α,β-Diamino-γ-Piperonylbutyric acid

DL-α-Amino-β-N-benzoylaminopiperonylbutyric acid (3.26 g; 0.1 mol) was added to barium hydroxide solution (15%, 50 ml) and refluxed for 24 hr. The mixture was left overnight at room temperature. Next morning benzoic acid crystallised out was filtered and washed with three 10 ml portions of water. The filtrate and washings were combined and evaporated to dryness under diminished pressure. The residue then taken in 20 ml of water neutralised cautiously with dilute sulphuric acid. The precipitated barium sulphate was filtered and washed with water. The combined filtrate and washing was evaporated under reduced pressure and the residue thus obtained was crystallised using ethanol (50%). This was filtered and dried. Yield 1.55 g (65%), m.p. 204°; UV λ_{max}^{MeOH} 260 nm; IR (Nujol) 2780, 2650, 1620, 1580, 1505, 1375 cm^{-1}.

Anal. for $C_{11}H_{14}O_4N_2$

Calcd: C, 55.45; H, 5.92; N, 11.76.

Found: C, 55.41; H, 5.88; N, 11.72.

17. Synthesis of DL-α,β-Diamino-γ-indolylbutyric acid

DL-α-Amino-β-N-benzoylamineindolylbutyric acid (3.23 g; 0.1 mol) was refluxed with barium hydroxide solution (50 ml, 15%), for 18 hr. At the end of this period benzoic acid was separated, washed with water and it was neutralised using dilute sulphuric acid. The precipitated barium sulphate was filtered and washed with three 20 ml portions of water. The combined filtrate and washings was evaporated to dryness under reduced pressure and the residue so obtained was crystallised from aqueous ethanol (50%). The amino acid obtained weighed 1.63 g (70%) and melted at 216°; UV λ_{max}^{MeOH} 230, 260 nm; IR (Nujol) 3030, 2770, 1720, 1640, 1610, 1560, 1480, 1340, 1270, 1230 cm^{-1}.

Anal. for $C_{12}H_{15}O_2N_3$

Calcd: C, 61.78; H, 6.48; N, 18.02.

Found: C, 61.76; H, 6.44; N, 18.00.

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